Example 15

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

In accordance with the present invention, a series of oligonucleotides were designed to target different regions of the human apolipoprotein B RNA, using published sequence (GenBank accession number NM_000384, incorporated herein as SEQ ID NO: 3). The oligonucleotides are shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 1 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 1

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	%INHIB	SEQ ID NO
147780	5'UTR	3	1	CCGCAGGTCCCGGTGGGAAT	40	17
147781	5'UTR	3	21	ACCGAGAAGGGCACTCAGCC	35	18
147782	5'UTR	3	71	GCCTCGGCCTCGCGGCCCTG	67	19

147783	Start Codon	3	114	TCCATCGCCAGCTGCGGTGG	N.D.	20
147784	Coding	3	151	CAGCGCCAGCAGCGCCAGCA	70	21
147785	Coding	3	181	GCCCGCCAGCAGCAGCAGCA	29	22
147786	Coding	3	321	CTTGAATCAGCAGTCCCAGG	34	23
147787	Coding	3	451	CTTCAGCAAGGCTTTGCCCT	N.D.	24
147788	Coding	3	716	TTTCTGTTGCCACATTGCCC	95	25
147789	Coding	3	911	GGAAGAGGTGTTGCTCCTTG	24	26
147790	Coding	3	951	TGTGCTACCATCCCATACTT	33	27
147791	Coding	3	1041	TCAAATGCGAGGCCCATCTT	N.D.	28
147792	Coding	3	1231	GGACACCTCAATCAGCTGTG	26	29
147793	Coding	3	1361	TCAGGGCCACCAGGTAGGTG	N.D.	30
147794	Coding	3	1561	GTAATCTTCATCCCCAGTGC	47	31
147795	Coding	3	1611	TGCTCCATGGTTTGGCCCAT	N.D.	32
147796	Coding	3	1791	GCAGCCAGTCGCTTATCTCC	8	33
147797	Coding	3	2331	GTATAGCCAAAGTGGTCCAC	N.D.	34
147798	Coding	3	2496	CCCAGGAGCTGGAGGTCATG	N.D.	35
147799	Coding	3	2573	TTGAGCCCTTCCTGATGACC	N.D.	36
147800	Coding	3	2811	ATCTGGACCCCACTCCTAGC	N.D.	37
147801	Coding	3	2842	CAGACCCGACTCGTGGAAGA	38	38
147802	Coding	3	3367	GCCCTCAGTAGATTCATCAT	N.D.	39
147803	Coding	3	3611	GCCATGCCACCCTCTTGGAA	N.D.	40
147804	Coding	3	3791	AACCCACGTGCCGGAAAGTC	N.D.	41
147805	Coding	3	3841	ACTCCCAGATGCCTTCTGAA	N.D.	42
147806	Coding	3	4281	ATGTGGTAACGAGCCCGAAG	100	43
147807	Coding	3	4391	GGCGTAGAGACCCATCACAT	25	44
147808	Coding	3	4641	GTGTTAGGATCCCTCTGACA	N.D.	45
147809	Coding	3	5241	CCCAGTGATAGCTCTGTGAG	60	46
147810	Coding	3	5355	ATTTCAGCATATGAGCCCAT	0	47
147811	Coding	3	5691	CCCTGAACCTTAGCAACAGT	N.D.	48
147812	Coding	3	5742	GCTGAAGCCAGCCCAGCGAT	N.D.	49
147813	Coding	3	5891	ACAGCTGCCCAGTATGTTCT	N.D.	50
147814	Coding	3	7087	CCCAATAAGATTTATAACAA	34	51
147815	Coding	3	7731	TGGCCTACCAGAGACAGGTA	45	52
147816	Coding	3	7841	TCATACGTTTAGCCCAATCT	100	53
147817	Coding	3	7901	GCATGGTCCCAAGGATGGTC	0	54
147818	Coding	3	8491	AGTGATGGAAGCTGCGATAC	30	55
147819	Coding	3	9181	ATGAGCATCATGCCTCCCAG	N.D.	56
147820	Coding	3	9931	GAACACATAGCCGAATGCCG	100	57
147821	Coding	3	10263	GTGGTGCCCTCTAATTTGTA	N.D.	58
147822	Coding	3	10631	CCCGAGAAAGAACCGAACCC	N.D.	59
147823	Coding	3	10712	TGCCCTGCAGCTTCACTGAA	19	60
147824	Coding	3	11170	GAAATCCCATAAGCTCTTGT	N.D.	61
147825	Coding	3	12301	AGAAGCTGCCTCTTCTTCCC	72	62
147826	Coding	3	12401	TCAGGGTGAGCCCTGTGTGT	80	63
147827	Coding	3	12471	CTAATGGCCCCTTGATAAAC	13	64
147828	Coding	3	12621	ACGTTATCCTTGAGTCCCTG	12	65
147829	Coding	3	12741	TATATCCCAGGTTTCCCCGG	64	66
147830	Coding	3	12801	ACCTGGGACAGTACCGTCCC	N.D.	67
147831	3'UTR	3	13921	CTGCCTACTGCAAGGCTGGC	0	68
147832	3'UTR	3	13991	AGAGACCTTCCGAGCCCTGG	N.D.	69
147833	3'UTR	3	14101	ATGATACACAATAAAGACTC	25	70

As shown in Table 1, SEQ ID NOs 17, 18, 19, 21, 23, 25, 27, 31, 38, 43, 46, 51, 52, 53, 55, 57, 62, 63 and 66 demonstrated at least 30% inhibition of human apolipoprotein B expression in this assay and are therefore preferred. The target sites to which these preferred sequences are complementary are herein referred to as "active sites" and are therefore preferred sites for targeting by compounds of the present invention. As apolipoprotein B exists in two forms in mammals (ApoB-48 and ApoB-100) which are colinear at the amino terminus, antisense oligonucleotides targeting nucleotides 1-6530 hybridize to both forms, while those targeting nucleotides 6531-14121 are specific to the long form of apolipoprotein B.

Example 16

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap-Dose Response Study

In accordance with the present invention, a subset of the antisense oligonuclotides in Example 15 were further investigated in dose-response studies. Treatment doses were 50, 150 and 250 nM. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments and are shown in Table 2.

Table 2

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

	Percent Inhibition		
ISIS #	50 nM	150 nM	250 nM
147788	54	63	72
147806	23	45	28
147816	25	81	65
147820	10	0	73

Example 17

Antisense inhibition of mouse apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

In accordance with the present invention, a series of oligonucleotides were designed to target different regions of the mouse apolipoprotein B RNA, using published sequence (GenBank accession number M35186, incorporated herein as SEQ ID NO: 10). The oligonucleotides are shown in Table 3. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 3 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on mouse apolipoprotein B mRNA levels in primary hepatocytes by quantitative real-time PCR as described in other examples herein. Data are averages

from two experiments. If present, "N.D." indicates "no data".

Table 3

Inhibition of mouse apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	%INHIB	SEQ ID NO
147475	Coding	10	13	ATTGTATGTGAGAGGTGAGG	79	71
147476	Coding	10	66	GAGGAGATTGGATCTTAAGG	13	72
147477	Coding	10	171	CTTCAAATTGGGACTCTCCT	N.D	73
147478	Coding	10	211	TCCAGGAATTGAGCTTGTGC	78	74
147479	Coding	10	238	TTCAGGACTGGAGGATGAGG	N.D	75
147480	Coding	10	291	TCTCACCCTCATGCTCCATT	54	76
147481	Coding	10	421	TGACTGTCAAGGGTGAGCTG	24	77
147482	Coding	10	461	GTCCAGCCTAGGAACACTCA	59	78
147483	Coding	10	531	ATGTCAATGCCACATGTCCA	N.D	79
147484	Coding	10	581	TTCATCCGAGAAGTTGGGAC	49	80
147485	Coding	10	601	ATTTGGGACGAATGTATGCC	64	81
147486	Coding	10	711	AGTTGAGGAAGCCAGATTCA	N.D	82
147487	Coding	10	964	TTCCCAGTCAGCTTTAGTGG	73	83
147488	Coding	10	1023	AGCTTGCTTGTTGGGCACGG	72	84
147489	Coding	10	1111	CCTATACTGGCTTCTATGTT	5	85
147490	Coding	10	1191	TGAACTCCGTGTAAGGCAAG	N.D	86
147491	Coding	10	1216	GAGAAATCCTTCAGTAAGGG	71	87
147492	Coding	10	1323	CAATGGAATGCTTGTCACTG	68	88
147493	Coding	10	1441	GCTTCATTATAGGAGGTGGT	41	89
147494	Coding	10	1531	ACAACTGGGATAGTGTAGCC	84	90
147495	Coding	10	1631	GTTAGGACCAGGGATTGTGA	0	91
147496	Coding	10	1691	ACCATGGAAAACTGGCAACT	19	92
147497	Coding	10	1721	TGGGAGGAAAAACTTGAATA	N.D	93
147498	Coding	10	1861	TGGGCAACGATATCTGATTG	0	94
147499	Coding	10	1901	CTGCAGGGCGTCAGTGACAA	29	95
147500	Coding	10	1932	GCATCAGACGTGATGTTCCC	N.D	96
147501	Coding	10	2021	CTTGGTTAAACTAATGGTGC	18	97
147502	Coding	10	2071	ATGGGAGCATGGAGGTTGGC	16	98
147503	Coding	10	2141	AATGGATGATGAAACAGTGG	26	99
147504	Coding	10	2201	ATCAATGCCTCCTGTTGCAG	N.D	100
147505	Coding	10	2231	GGAAGTGAGACTTTCTAAGC	76	101
147506	Coding	10	2281	AGGAAGGAACTCTTGATATT	58	102
147507	Coding	10	2321	ATTGGCTTCATTGGCAACAC	81	103
147759	Coding	10	1	AGGTGAGGAAGTTGGAATTC	19	104
147760	Coding	10	121	TTGTTCCCTGAAGTTGTTAC	N.D	105
147761	Coding	10	251	GTTCATGGATTCCTTCAGGA	45	106
147762	Coding	10	281	ATGCTCCATTCTCACATGCT	46	107
147763	Coding	10	338	TGCGACTGTGTCTGATTTCC	34	108
147764	Coding	10	541	GTCCCTGAAGATGTCAATGC	97	109
147765	Coding	10	561	AGGCCCAGTTCCATGACCCT	59	110
147766	Coding	10	761	GGAGCCCACGTGCTGAGATT	59	111

147767	Coding	10	801	CGTCCTTGAGCAGTGCCCGA	5	112
147768	Coding	10	1224	CCCATATGGAGAAATCCTTC	24	113
147769	Coding	10	1581	CATGCCTGGAAGCCAGTGTC	89	114
147770	Coding	10	1741	GTGTTGAATCCCTTGAAATC	67	115
147771	Coding	10	1781	GGTAAAGTTGCCCATGGCTG	68	116
147772	Coding	10	1841	GTTATAAAGTCCAGCATTGG	78	117
147773	Coding	10	1931	CATCAGACGTGATGTTCCCT	85	118
147774	Coding	10	1956	TGGCTAGTTTCAATCCCCTT	84	119
147775	Coding	10	2002	CTGTCATGACTGCCCTTTAC	52	120
147776	Coding	10	2091	GCTTGAAGTTCATTGAGAAT	92	121
147777	Coding	10	2291	TTCCTGAGAAAGGAAGGAAC	N.D	122
147778	Coding	10	2331	TCAGATATACATTGGCTTCA	14	123

As shown in Table 3, SEQ ID Nos 71, 74, 76, 78, 81, 83, 84, 87, 88, 90, 101, 102, 103, 109, 111, 111, 114, 115, 116, 117, 118, 119, 120 and 121 demonstrated at least 50% inhibition of mouse apolipoprotein B expression in this assay and are therefore preferred. The target sites to which these preferred sequences are complementary are herein referred to as "active sites" and are therefore preferred sites for targeting by compounds of the present invention.

Example 18

Antisense inhibition mouse apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap- Dose Response Study

In accordance with the present invention, a subset of the antisense oligonuclotides in Example 17 were further investigated in dose-response studies. Treatment doses were 50, 150 and 300 nM. The compounds were analyzed for their effect on mouse apolipoprotein B mRNA levels in primary hepatocytes cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments and are shown in Table 4.

Table 4

Inhibition of mouse apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

	Percent Inhibition		
ISIS #	50 nM	150 nM	300 nM
147483	56	88	89
147764	48	84	90
147769	3	14	28
147776	0	17	44

Example 19

Western blot analysis of apolipoprotein B protein levels

Western blot analysis (immunoblot analysis) was carried out using standard methods. Cells were harvested 16-20 h after oligonucleotide treatment, washed once with PBS, suspended in Laemmli buffer (100 ul/well), boiled for 5 minutes and loaded on a 16% SDS-PAGE gel. Gels were run for 1.5 hours at 150 V, and transferred to membrane for western blotting. Appropriate primary antibody directed to apolipoprotein B was used, with a radiolabelled or fluorescently labeled secondary antibody directed against the primary antibody species. Bands were visualized using a PHOSPHORIMAGER™ (Molecular Dynamics, Sunnyvale CA).

Example 20

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) in C57BL/6 mice: Lean animals vs. High Fat Fed animals.

C57BL/6 mice, a strain reported to be susceptible to hyperlipidemia-induced atherosclerotic plaque formation were used in the following studies to evaluate antisense oligonucleotides as potential lipid lowering compounds in lean versus high fat fed mice.

Male C57BL/6 mice were divided into two matched groups; (1) wild-type control animals (lean animals) and (2) animals receiving a high fat diet (60% kcal fat). Control animals received saline treatment and were maintained on a normal rodent diet. After overnight fasting, mice from each group were dosed intraperitoneally every three days with saline or 50 mg/kg ISIS 147764 (SEQ ID No: 109) for six weeks. At study termination and forty eight hours after the final injections, animals were sacrificed and evaluated for target mRNA levels in liver, cholesterol and triglyceride levels, liver enzyme levels and serum glucose levels.

The results of the comparative studies are shown in Table 5.

Table 5

Effects of ISIS 147764 treatment on apolipoprotein B mRNA, cholesterol, lipid, triglyceride, liver enzyme and glucose levels in lean and high fat mice.

Treatment Group	Percent Change								
			Lipoproteins				Liver Enzymes		
	mRNA	CHOL	VLDL	LDL	HDL	TRIG	AST	ALT	GLUC
Lean-control	-73	-63	No change	-64	-44	-34	Slight decrease	No change	No change
High Fat Group	-87	-67	No change	-87	-65	No change	Slight decrease	Slight increase	-28

It is evident from these data that treatment with ISIS 147764 lowered cholesterol as well as LDL and HDL lipoproteins and serum glucose in both lean and high fat mice and that the effects demonstrated are, in fact, due to the inhibition of apolipoprotein B expression as supported by the decrease in mRNA levels. No significant changes in liver enzyme levels were observed, indicating that the

antisense oligonucleotide was not toxic to either treatment group.

Example 21

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) on High Fat Fed Mice; 6 Week Timecourse Study

In accordance with the present invention, a 6-week timecourse study was performed to further investigate the effects of ISIS 147764 on lipid and glucose metabolism in high fat fed mice.

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of treatment with the antisense oligonucleotide, ISIS 147764. Control animals received saline treatment (50 mg/kg). A subset of animals received a daily oral dose (20 mg/kg) atorvastatin calcium (Lipitor®, Pfizer Inc.). All mice, except atorvastatin-treated animals, were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50 mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks. Serum cholesterol and lipoproteins were analyzed at 0, 2 and 6 week interim timepoints. At study termination, animals were sacrificed 48 hours after the final injections and evaluated for levels of target mRNA levels in liver, cholesterol, lipoprotein, triglyceride, liver enzyme (AST and ALT) and serum glucose levels as well as body, liver, spleen and fat pad weights.

Example 22

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) in high fat fed mice- mRNA expression in liver

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of ISIS 147764 on mRNA expression. Control animals received saline treatment (50 mg/kg). Mice were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50 mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks. At study termination, animals were sacrificed 48 hours after the final injections and evaluated for levels of target mRNA levels in liver. ISIS 147764 showed a dose-response effect, reducing mRNA levels by 15, 75 and 88% at doses of 5, 25 and 50 mg/kg, respectively.

Example 23

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) on serum cholesterol and triglyceride levels

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of ISIS 147764 on serum cholesterol and triglyceride levels. Control animals received saline treatment (50 mg/kg). Mice were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50 mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks.

Serum cholesterol levels were measured at 0, 2 and 6 weeks and this data is shown in Table 6. Values in the table are expressed as percent inhibition and are normalized to the saline control.

In addition to serum cholesterol, at study termination, animals were sacrificed 48 hours after the final injections and evaluated for triglyceride levels.

Mice treated with ISIS 147764 showed a reduction in both serum cholesterol (240 mg/dL for control animals and 225, 125 and 110 mg/dL for doses of 5, 25, and 50 mg/kg, respectively) and triglycerides (115 mg/dL for control animals and 125, 150 and 85 mg/dL for doses of 5, 25, and 50 mg/kg, respectively) to normal levels by study end. These data were also compared to the effects of atorvastatin calcium at an oral dose of 20 mg/kg which showed only a minimal decrease in serum cholesterol of 20 percent at study termination.

Table 6

Percent Inhibition of mouse apolipoprotein B cholesterol levels by ISIS 147764

	Percent Inhibition			
time	Saline	5 mg/kg	25 mg/kg	50 mg/kg
0 weeks	0	0	0	0
2 weeks	0	5	12	20
6 weeks	0	10	45	55

Example 24

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) on lipoprotein levels

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of ISIS 147764 on lipoprotein (VLDL, LDL and HDL) levels. Control animals received saline treatment (50 mg/kg). Mice were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50 mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks.

Lipoprotein levels were measured at 0, 2 and 6 weeks and this data is shown in Table 7. Values in the table are expressed as percent inhibition and are normalized to the

saline control. Negative values indicate an observed increase in lipoprotein levels.

These data were also compared to the effects of atorvastatin calcium at a daily oral dose of 20 mg/kg at 0, 2 and 6 weeks.

These data demonstrate that at a dose of 50 mg/kg, ISIS 147764 is capable of lowering all categories of serum lipoproteins investigated to a greater extent than atorvastatin.

Table 7

Percent Inhibition of mouse apolipoprotein B lipoprotein levels by ISIS 147764 as compared to atorvastatin

		Percent Inhibition				
		Dose				
Lipoprotein	Time (weeks)	Saline	5 mg/kg	25 mg/kg	50 mg/kg	atorvastatin (20 mg/kg)
VLDL	0	0	0	0	0	0
	2	0	25	30	40	15
	6	0	10	-30	15	-5
LDL	0	0	0	0	0	0
	2	0	-30	10	40	10
	6	0	-10	55	90	-10
HDL	0	0	0	0	0	0
	2	0	5	10	10	15
	6	0	10	45	50	20

Example 25

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) on serum AST and ALT levels

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of ISIS 147764 on liver enzyme (AST and ALT) levels. Control animals received saline treatment (50 mg/kg). Mice were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50

mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks.

AST and ALT levels were measured at 6 weeks and this data is shown in Table 8. Values in the table are expressed as IU/L. Increased levels of the liver enzymes ALT and AST indicate toxicity and liver damage.

Mice treated with ISIS 147764 showed no significant change in AST levels over the duration of the study compared to saline controls (105, 70 and 80 IU/L for doses of 5, 25 and 50 mg/kg, respectively compared to 65 IU/L for saline control). Mice treated with atorvastatin at a daily oral dose of 20 mg/kg had AST levels of 85 IU/L.

ALT levels were increased by all treatments over the duration of the study compared to saline controls (50, 70 and 100 IU/L for doses of 5, 25 and 50 mg/kg, respectively compared to 25 IU/L for saline control). Mice treated with atorvastatin at a daily oral dose of 20 mg/kg had AST levels of 40 IU/L.

Example 26

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) on serum glucose levels

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of ISIS 147764 on serum glucose levels. Control animals received saline treatment (50 mg/kg). Mice were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50 mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks.

At study termination, animals were sacrificed 48 hours after the final injections and evaluated for serum glucose levels. ISIS 147764 showed a dose-response effect, reducing

serum glucose levels to 225, 190 and 180 mg/dL at doses of 5, 25 and 50 mg/kg, respectively compared to the saline control of 300 mg/dL. Mice treated with atorvastatin at a daily oral dose of 20 mg/kg had serum glucose levels of 215 mg/dL. These data demonstrate that ISIS 147764 is capable of reducing serum glucose levels in high fat fed mice.

Example 27

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) on body, spleen, liver and fat pad weight

Male C57BL/6 mice (n=8) receiving a high fat diet (60% kcal fat) were evaluated over the course of 6 weeks for the effects of ISIS 147764 on body, spleen, liver and fat pad weight. Control animals received saline treatment (50 mg/kg). Mice were dosed intraperitoneally every three days (twice a week), after fasting overnight, with 5, 25, 50 mg/kg ISIS 147764 (SEQ ID No: 109) or saline (50 mg/kg) for six weeks.

At study termination, animals were sacrificed 48 hours after the final injections and body, spleen, liver and fat pad weights were measured. These data are shown in Table 8. Values are expressed as percent change in body weight or ogan weight compared to the saline-treated control animals. Data from mice treated with atorvastatin at a daily dose of 20 mg/kg are also shown in the table. Negative values indicated a decrease in weight.

Table 8

Effects of antisense inhibition of mouse apolipoprotein B on body and organ weight

	Percent Change			
	Dose			Atorvastatin 20 mg/kg
Tissue	5 mg/kg	25 mg/kg	50 mg/kg	
Total Body Wt.	5	5	-4	1
Spleen	10	10	46	10
Liver	18	70	80	15
Fat	10	6	-47	7

These data show a decrease in fat over the dosage range of ISIS 147764 counterbalanced by an increase in both spleen and liver weight with increased dose to give an overall decrease in total body weight.

Example 28

Effects of antisense inhibition of apolipoprotein B (ISIS 147764) in B6.129P-Apoe^{tm1Unc} knockout mice: Lean animals vs. High Fat Fed animals.

B6.129P-ApoE^{tm1Unc} knockout mice (herein referred to as ApoE knockout mice) obtained from The Jackson Laboratory (Bar Harbor, ME), are homozygous for the *Apoe*^{tm1Unc} mutation and show a marked increase in total plasma cholesterol levels that are unaffected by age or sex. These animals present with fatty streaks in the proximal aorta at 3 months of age. These lesions increase with age and progress to lesions with less lipid but more elongated cells, typical of a more advanced stage of pre-atherosclerotic lesion.

The mutation in these mice resides in the apolipoprotein E (ApoE) gene. The primary role of the ApoE protein is to transport cholesterol and triglycerides throughout the body. It stabilizes lipoprotein structure, binds to the low density lipoprotein receptor (LDLR) and related proteins, and is present in a subclass of HDLs, providing them the ability to bind to LDLR. ApoE is

expressed most abundantly in the liver and brain. Female B6.129P-Apoetm1Unc knockout mice (ApoE knockout mice) were used in the following studies to evaluate antisense oligonucleotides as potential lipid lowering compounds.

Female ApoE knockout mice ranged in age from 5 to 7 weeks and were placed on a normal diet for 2 weeks before study initiation. ApoE knockout mice were then fed *ad libitum* a 60% fat diet, with 0.15% added cholesterol to induce dyslipidemia and obesity. Control animals were maintained on a high-fat diet with no added cholesterol. After overnight fasting, mice from each group were dosed intraperitoneally every three days with saline, 50 mg/kg of a control antisense oligonucleotide (ISIS 29837 TCGATCTCCTTTTATGCCCG; SEQ ID NO. 124) or 5, 25 or 50 mg/kg ISIS 147764 (SEQ ID No: 109) for six weeks.

The control oligonucleotide is a chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines.

At study termination and forty eight hours after the final injections, animals were sacrificed and evaluated for target mRNA levels in liver by RT-PCR methods verified by Northern Blot analysis, glucose levels, cholesterol and lipid levels by HPLC separation methods and triglyceride and liver enzyme levels (perfomed by LabCorp Preclinical Services; San Diego, CA). Data from ApoE knockout mice

treated with atorvastatin at a daily dose of 20 mg/kg are also shown in the table for comparison.

The results of the comparative studies are shown in Table 9. Data are normalized to saline controls.

Table 9

Effects of ISIS 147764 treatment on apolipoprotein B mRNA, cholesterol, glucose, lipid, triglyceride and liver enzyme levels in ApoE knockout mice.

		Percent Inhibition				
		Dose				
		Control	5 mg/kg	25 mg/kg	50 mg/kg	atorvastatin (20 mg/kg)
mRNA		0	2	42	70	10
Glucose		Glucose Levels (mg/dL)				
		225	195	209	191	162
		Cholesterol Levels (mg/dL)				
Cholesterol		1750	1630	1750	1490	938
		Lipoprotein Levels (mg/dL)				
Lipoprotein	HDL	51	49	62	61	42
	LDL	525	475	500	325	250
	VLDL	1190	1111	1194	1113	653
		Liver Enzyme Levels (IU/L)				
Liver Enzymes	AST	55	50	60	85	75
	ALT	56	48	59	87	76

It is evident from these data that treatment with ISIS 147764 lowered glucose and cholesterol as well as all lipoproteins investigated (HDL, LDL and VLDL) in ApoE knockout mice. Further, these decreases correlated with a decrease in both protein and RNA levels of apolipoprotein B, demonstrating an antisense mechanism of action. No

significant changes in liver enzyme levels were observed, indicating that the antisense oligonucleotide was not toxic to either treatment group.

Example 29

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap: Additional Oligonucleotides

In accordance with the present invention, another series of oligonucleotides were designed to target different regions of the human apolipoprotein B RNA, using published sequence (GenBank accession number NM_000384.1, incorporated herein as SEQ ID NO: 3). The oligonucleotides are shown in Table 10.

Table 10

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB	SEQ ID NO
270985	5'UTR	3	199	TTCCTCTTCGGCCCTGGCGC	75	124
270986	coding	3	299	CTCCACTGGAACTCTCAGCC	0	125
270987	exon: exon junction	3	359	CCTCCAGCTCAACCTTGCAG	0	126
270988	coding	3	429	GGGTTGAAGCCATACACCTC	6	127
270989	exon: exon junction	3	509	CCAGCTTGAGCTCATACCTG	64	128
270990	coding	3	584	CCCTCTTGATGTTCAGGATG	42	129

270991	coding	3	669	GAGCAGTTTCCATACACGGT	21	130
270992	coding	3	699	CCCTTCCTCGTCTTGACGGT	8	131
270993	coding	3	756	TTGAAGCGATCACACTGCCC	69	132
270994	coding	3	799	GCCTTTGATGAGAGCAAGTG	51	133
270995	coding	3	869	TCCTCTTAGCGTCCAGTGTG	40	134
270996	coding	3	1179	CCTCTCAGCTCAGTAACCAG	0	135
270997	coding	3	1279	GCACTGAGGCTGTCCACACT	24	136
270998	coding	3	1419	CGCTGATCCCTCGCCATGTT	1	137
270999	coding	3	1459	GTTGACCGCGTGGCTCAGCG	76	138
271000	coding	3	1499	GCAGCTCCTGGGTCCCTGTA	22	139
271001	coding	3	1859	CCCATGGTAGAATTTGGACA	53	140
271002	exon: exon junction	3	2179	AATCTCGATGAGGTCAGCTG	48	141
271003	coding	3	2299	GACACCATCAGGAACTTGAC	46	142
271004	coding	3	2459	GCTCCTCTCCCAAGATGCGG	10	143
271005	coding	3	2518	GGCACCCATCAGAAGCAGCT	32	144
271006	coding	3	2789	AGTCCGGAATGATGATGCCC	42	145
271007	coding	3	2919	CTGAGCAGCTTGACTGGTCT	26	146
271008	coding	3	3100	CCCGGTCAGCGGATAGTAGG	37	147
271010	exon: exon junction	3	3449	TGTCACAACTTAGGTGGCCC	57	148
271011	coding	3	3919	GTCTGGCAATCCCATGTTCT	51	149
271012	coding	3	4089	CCCACAGACTTGAAGTGGAG	55	150
271013	coding	3	4579	GAACTGCCCATCAATCTTGA	19	151
271014	coding	3	5146	CCCAGAGAGGCCAAGCTCTG	54	152
271015	coding	3	5189	TGTGTTCCCTGAAGCGGCCA	43	153
271016	coding	3	5269	ACCCAGAATCATGGCCTGAT	19	154
271017	coding	3	6049	GGTGCCTGTCTGCTCAGCTG	30	155
271018	coding	3	6520	ATGTGAAACTTGTCTCTCCC	44	156
271019	coding	3	6639	TATGTCTGCAGTTGAGATAG	15	157
271020	coding	3	6859	TTGAATCCAGGATGCAGTAC	35	158
271021	coding	3	7459	GAGTCTCTGAGTCACCTCAC	38	159
271022	coding	3	7819	GATAGAATATTGCTCTGCAA	100	160
271023	coding	3	7861	CCCTTGCTCTACCAATGCTT	44	161
271025	coding	3	8449	TCCATTCCCTATGTCAGCAT	16	162
271026	coding	3	8589	GACTCCTTCAGAGCCAGCGG	39	163
271027	coding	3	8629	CCCATGCTCCGTTCTCAGGT	26	164
271028	coding	3	8829	CGCAGGTCAGCCTGACTAGA	98	165
271030	coding	3	9119	CAGTTAGAACACTGTGGCCC	52	166
271031	coding	3	10159	CAGTGTGATGACACTTGATT	49	167
271032	coding	3	10301	CTGTGGCTAACTTCAATCCC	22	168
271033	coding	3	10349	CAGTACTGTTATGACTACCC	34	169
271034	coding	3	10699	CACTGAAGACCGTGTGCTCT	35	170
271035	coding	3	10811	TCGTACTGTGCTCCCAGAGG	23	171
271036	coding	3	10839	AAGAGGCCCTCTAGCTGTAA	95	172
271037	coding	3	11039	AAGACCCAGAATGAATCCGG	23	173
271038	coding	3	11779	GTCTACCTCAAAGCGTGCAG	29	174
271039	coding	3	11939	TAGAGGCTAACGTACCATCT	4	175
271041	coding	3	12149	CCATATCCATGCCCACGGTG	37	176

271042	coding	3	12265	AGTTTCCTCATCAGATTCCC	57	177
271043	coding	3	12380	CCCAGTGGTACTTGTTGACA	68	178
271044	coding	3	12526	CCCAGTGGTGCCACTGGCTG	22	179
271045	coding	3	12579	GTCAACAGTTCCTGGTACAG	19	180
271046	coding	3	12749	CCCTAGTGTATATCCCAGGT	61	181
271048	coding	3	13009	CTGAAGATTACGTAGCACCT	7	182
271049	coding	3	13299	GTCCAGCCAACTATACTTGG	54	183
271050	coding	3	13779	CCTGGAGCAAGCTTCATGTA	42	184
281586	exon: exon junction	3	229	TGGACAGACCAGGCTGACAT	80	185
281587	coding	3	269	ATGTGTACTTCCGGAGGTGC	77	186
281588	coding	3	389	TCTTCAGGATGAAGCTGCAG	80	187
281589	coding	3	449	TCAGCAAGGCTTTGCCCTCA	90	188
281590	coding	3	529	CTGCTTCCCTTCTGGAATGG	84	189
281591	coding	3	709	TGCCACATTGCCCTTCCTCG	90	190
281592	coding	3	829	GCTGATCAGAGTTGACAAGG	56	191
281593	coding	3	849	TACTGACAGGACTGGCTGCT	93	192
281594	coding	3	889	GATGGCTTCTGCCACATGCT	74	193
281595	coding	3	1059	GATGTGGATTTGGTGCTCTC	76	194
281596	coding	3	1199	TGACTGCTTCATCACTGAGG	77	195
281597	coding	3	1349	GGTAGGTGACCACATCTATC	36	196
281598	coding	3	1390	TCGCAGCTGCTGTGCTGAGG	70	197
281599	exon: exon junction	3	1589	TTCCAATGACCCGCAGAATC	74	198
281600	coding	3	1678	GATCATCAGTGATGGCTTTG	52	199
281601	coding	3	1699	AGCCTGGATGGCAGCTTTCT	83	200
281602	coding	3	1749	GTCTGAAGAAGAACCTCCTG	84	201
281603	coding	3	1829	TATCTGCCTGTGAAGGACTC	82	202
281604	coding	3	1919	CTGAGTTCAAGATATTGGCA	78	203
281605	exon: exon junction	3	2189	CTTCCAAGCCAATCTCGATG	82	204
281606	coding	3	2649	TGCAACTGTAATCCAGCTCC	86	205
281607	exon: exon junction	3	2729	CCAGTTCAGCCTGCATGTTG	84	206
281608	coding	3	2949	GTAGAGACCAAATGTAATGT	62	207
281609	coding	3	3059	CGTTGGAGTAAGCGCCTGAG	70	208
281610	exon: exon junction	3	3118	CAGCTCTAATCTGGTGTCCC	69	209
281611	coding	3	3189	CTGTCCTCTCTCTGGAGCTC	93	210
281612	coding	3	3289	CAAGGTCATACTCTGCCGAT	83	211
281613	coding	3	3488	GTATGGAAATAACACCCTTG	70	212
281614	coding	3	3579	TAAGCTGTAGCAGATGAGTC	63	213
281615	coding	3	4039	TAGATCTCTGGAGGATTTGC	81	214
281616	coding	3	4180	GTCTAGAACACCCAGGAGAG	66	215
281617	coding	3	4299	ACCACAGAGTCAGCCTTCAT	89	216
281618	coding	3	4511	AAGCAGACATCTGTGGTCCC	90	217
281619	coding	3	4660	CTCTCCATTGAGCCGGCCAG	96	218

281620	coding	3	4919	CCTGATATTCAGAACGCAGC	89	219
281621	coding	3	5009	CAGTGCCTAAGATGTCAGCA	53	220
281622	coding	3	5109	AGCACCAGGAGACTACACTT	88	221
281623	coding	3	5212	CCCATCCAGACTGAATTTTG	59	222
281624	coding	3	5562	GGTTCTAGCCGTAGTTTCCC	75	223
281625	coding	3	5589	AGGTTACCAGCCACATGCAG	94	224
281626	coding	3	5839	ATGTGCATCGATGGTCATGG	88	225
281627	coding	3	5869	CCAGAGAGCGAGTTTCCCAT	82	226
281628	coding	3	5979	CTAGACACGAGATGATGACT	81	227
281629	coding	3	6099	TCCAAGTCCTGGCTGTATTC	83	228
281630	coding	3	6144	CGTCCAGTAAGCTCCACGCC	82	229
281631	coding	3	6249	TCAACGGCATCTCTCATCTC	88	230
281632	coding	3	6759	TGATAGTGCTCATCAAGACT	75	231
281633	coding	3	6889	GATTCTGATTTGGTACTTAG	73	232
281634	coding	3	7149	CTCTCGATTAACTCATGGAC	81	233
281635	coding	3	7549	ATACACTGCAACTGTGGCCT	89	234
281636	coding	3	7779	GCAAGAGTCCACCAATCAGA	68	235
281637	coding	3	7929	AGAGCCTGAAGACTGACTTC	74	236
281638	coding	3	8929	TCCCTCATCTGAGAATCTGG	66	237
281640	coding	3	10240	CAGTGCATCAATGACAGATG	87	238
281641	coding	3	10619	CCGAACCCTTGACATCTCCT	72	239
281642	coding	3	10659	GCCTCACTAGCAATAGTTCC	59	240
281643	coding	3	10899	GACATTTGCCATGGAGAGAG	61	241
281644	coding	3	11209	CTGTCTCCTACCAATGCTGG	26	242
281645	exon: exon junction	3	11979	TCTGCACTGAAGTCACGGTG	78	243
281646	coding	3	12249	TCCCGGACCCTCAACTCAGT	76	244
281648	3'UTR	3	13958	GCAGGTCCAGTTCATATGTG	81	245
281649	3'UTR	3	14008	GCCATCCTTCTGAGTTCAGA	76	246
301012	exon: exon junction	3	3249	GCCTCAGTCTGCTTCGCACC	87	247
301013	5'UTR	3	3	CCCCGCAGGTCCCGGTGGGA	82	248
301014	5'UTR	3	6	CAGCCCCGCAGGTCCCGGTG	88	249
301015	5'UTR	3	23	CAACCGAGAAGGGCACTCAG	53	250
301016	5'UTR	3	35	CCTCAGCGGCAGCAACCGAG	62	251
301017	5'UTR	3	36	TCCTCAGCGGCAGCAACCGA	47	252
301018	5'UTR	3	37	CTCCTCAGCGGCAGCAACCG	45	253
301019	5'UTR	3	39	GGCTCCTCAGCGGCAGCAAC	70	254
301020	5'UTR	3	43	GGCGGGCTCCTCAGCGGCAG	85	255
301021	5'UTR	3	116	GGTCCATCGCCAGCTGCGGT	89	256
301022	Start Codon	3	120	GGCGGGTCCATCGCCAGCTG	69	257
301023	Stop Codon	3	13800	TAGAGGATGATAGTAAGTTC	69	258
301024	3'UTR	3	13824	AAATGAAGATTTCTTTTAAA	5	259
301025	3'UTR	3	13854	TATGTGAAAGTTCAATTGGA	76	260
301026	3'UTR	3	13882	ATATAGGCAGTTTGAATTTT	57	261
301027	3'UTR	3	13903	GCTCACTGTATGGTTTTATC	89	262
301028	3'UTR	3	13904	GGCTCACTGTATGGTTTTAT	93	263
301029	3'UTR	3	13908	GGCTGGCTCACTGTATGGTT	90	264

301030	3'UTR	3	13909	AGGCTGGCTCACTGTATGGT	90	265
301031	3'UTR	3	13910	AAGGCTGGCTCACTGTATGG	90	266
301032	3'UTR	3	13917	CTACTGCAAGGCTGGCTCAC	63	267
301033	3'UTR	3	13922	ACTGCCTACTGCAAGGCTGG	77	268
301034	3'UTR	3	13934	TGCTTATAGTCTACTGCCTA	88	269
301035	3'UTR	3	13937	TTCTGCTTATAGTCTACTGC	82	270
301036	3'UTR	3	13964	TTTGGTGCAGGTCCAGTTCA	88	271
301037	3'UTR	3	13968	CAGCTTTGGTGCAGGTCCAG	90	272
301038	3'UTR	3	13970	GCCAGCTTTGGTGCAGGTCC	86	273
301039	3'UTR	3	13974	TGGTGCCAGCTTTGGTGCAG	73	274
301040	3'UTR	3	13978	GCCCTGGTGCCAGCTTTGGT	74	275
301041	3'UTR	3	13997	GAGTTCAGAGACCTTCCGAG	85	276
301042	3'UTR	3	14012	AAATGCCATCCTTCTGAGTT	81	277
301043	3'UTR	3	14014	AAAAATGCCATCCTTCTGAG	81	278
301044	3'UTR	3	14049	AAAATAACTCAGATCCTGAT	76	279
301045	3'UTR	3	14052	AGCAAAATAACTCAGATCCT	90	280
301046	3'UTR	3	14057	AGTTTAGCAAAATAACTCAG	80	281
301047	3'UTR	3	14064	TCCCCCAAGTTTAGCAAAAT	56	282
301048	3'UTR	3	14071	TTCCTCCTCCCCCAAGTTTA	67	283
301217	3'UTR	3	14087	AGACTCCATTTATTTGTTCC	81	284

Example 30

Antisense inhibition of apolipoprotein B - Gene walk

In accordance with the present invention, a "gene walk" was conducted in which another series of oligonucleotides was designed to target the regions of the human apolipoprotein B RNA (GenBank accession number NM_000384.1, incorporated herein as SEQ ID NO: 3) which are near the target site of SEQ ID Nos 224 or 247. The oligonucleotides are shown in Table 11. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 10 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate

(P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 11

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Gene walk

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB 150 nM	% INHIB 50 nM	SEQ ID NO
308589	exon: exon junction	3	3230	CTTCTGCTTGAGTTACAAAC	94	20	285
308590	exon: exon junction	3	3232	ACCTTCTGCTTGAGTTACAA	98	26	286
308591	exon: exon junction	3	3234	GCACCTTCTGCTTGAGTTAC	92	76	287
308592	exon: exon junction	3	3236	TCGCACCTTCTGCTTGAGTT	96	49	288
308593	exon: exon junction	3	3238	CTTCGCACCTTCTGCTTGAG	80	41	289
308594	exon: exon junction	3	3240	TGCTTCGCACCTTCTGCTTG	88	57	290
308595	exon: exon junction	3	3242	TCTGCTTCGCACCTTCTGCT	82	60	291
308596	exon: exon junction	3	3244	AGTCTGCTTCGCACCTTCTG	94	81	292
308597	exon: exon junction	3	3246	TCAGTCTGCTTCGCACCTTC	91	66	293
308598	exon: exon junction	3	3248	CCTCAGTCTGCTTCGCACCT	85	59	294
308599	exon: exon junction	3	3250	AGCCTCAGTCTGCTTCGCAC	94	79	295

308600	coding	3	3252	GTAGCCTCAGTCTGCTTCGC	89	72	296
308601	coding	3	3254	TGGTAGCCTCAGTCTGCTTC	91	63	297
308602	coding	3	3256	CATGGTAGCCTCAGTCTGCT	92	83	298
308603	coding	3	3258	GTCATGGTAGCCTCAGTCTG	97	56	299
308604	coding	3	3260	ATGTCATGGTAGCCTCAGTC	90	73	300
308605	coding	3	3262	GAATGTCATGGTAGCCTCAG	81	50	301
308606	coding	3	3264	TTGAATGTCATGGTAGCCTC	97	54	302
308607	coding	3	3266	ATTTGAATGTCATGGTAGCC	77	9	303
308608	coding	3	3268	ATATTTGAATGTCATGGTAG	85	70	304
308609	coding	3	5582	CAGCCACATGCAGCTTCAGG	96	78	305
308610	coding	3	5584	ACCAGCCACATGCAGCTTCA	90	40	306
308611	coding	3	5586	TTACCAGCCACATGCAGCTT	95	59	307
308612	coding	3	5588	GGTTACCAGCCACATGCAGC	90	75	308
308613	coding	3	5590	TAGGTTACCAGCCACATGCA	87	43	309
308614	coding	3	5592	TTTAGGTTACCAGCCACATG	92	74	310
308615	coding	3	5594	CTTTTAGGTTACCAGCCACA	85	45	311
308616	coding	3	5596	TCCTTTTAGGTTACCAGCCA	81	39	312
308617	coding	3	5598	GCTCCTTTTAGGTTACCAGC	87	77	313
308618	coding	3	5600	AGGCTCCTTTTAGGTTACCA	77	61	314
308619	coding	3	5602	GTAGGCTCCTTTTAGGTTAC	74	69	315
308620	coding	3	5604	TGGTAGGCTCCTTTTAGGTT	88	69	316
308621	coding	3	5606	TTTGGTAGGCTCCTTTTAGG	91	56	317

As shown in Tables 10 and 11, SEQ ID Nos 124, 128, 129, 132, 133, 134, 138, 140, 141, 142, 144, 145, 147, 148, 149, 150, 152, 153, 155, 156, 158, 159, 160, 161, 163, 165, 166, 167, 169, 170, 172, 176, 177, 178, 181, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, and 317 demonstrated at least 30% inhibition of human

apolipoprotein B expression in this assay and are therefore preferred. More preferred are SEQ ID Nos 224, 247, and 262. The target regions to which these preferred sequences are complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 18. The sequences represent the reverse complement of the preferred antisense compounds shown in Tables 10 and 11. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 18 is the species in which each of the preferred target segments was found.

Example 31

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap: Targeting GenBank Accession number M14162.1

In accordance with the present invention, another series of oligonucleotides were designed to target different regions of the human apolipoprotein B RNA, using published sequence (GenBank accession number M14162.1, incorporated herein as SEQ ID NO: 318). The oligonucleotides are shown in Table 12. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 12 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are

composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 12

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB	SEQ ID NO
271009	coding	318	3121	GCCTCAGTCTGCTTCGCGCC	75	319
271024	coding	318	8031	GCTCACTGTTCAGCATCTGG	27	320
271029	coding	318	8792	TGAGAATCTGGGCGAGGCCC	N.D.	321
271040	coding	318	11880	GTCCTTCATATTTGCCATCT	0	322
271047	coding	318	12651	CCTCCCTCATGAACATAGTG	32	323
281639	coding	318	9851	GACGTCAGAACCTATGATGG	38	324
281647	coding	318	12561	TGAGTGAGTCAATCAGCTTC	73	325

Example 32

Antisense Inhibition of human apolipoprotein B - Gene walk targeting GenBank Accession number M14162.1

In accordance with the present invention, a "gene walk" was conducted in which another series of oligonucleotides were designed to target the regions of the human apolipoprotein B RNA (GenBank accession number M14162.1, incorporated herein as SEQ ID NO: 318) which are near the target site of SEQ ID NO: 319. The oligonucleotides are shown in Table 13. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide

binds. All compounds in Table 12 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 13

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB 150 nM	% INHIB 50 nM	SEQ ID NO
308622	coding	318	3104	GCCTTCTGCTTGAGTTACAA	87	25	326
308623	coding	318	3106	GCGCCTTCTGCTTGAGTTAC	71	62	327
308624	coding	318	3108	TCGCGCCTTCTGCTTGAGTT	89	69	328
308625	coding	318	3110	CTTCGCGCCTTCTGCTTGAG	83	64	329
308626	coding	318	3116	AGTCTGCTTCGCGCCTTCTG	94	38	330
308627	coding	318	3118	TCAGTCTGCTTCGCGCCTTC	89	67	331
308628	coding	318	3120	CCTCAGTCTGCTTCGCGCCT	92	61	332
308629	coding	318	3122	AGCCTCAGTCTGCTTCGCGC	95	77	333

As shown in Tables 12 and 13, SEQ ID Nos 319, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, and 333 demonstrated at least 30% inhibition of human apolipoprotein B expression in this assay and are therefore preferred. More preferred is SEQ ID NO: 319 . The target regions to which these preferred sequences are

complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 18. The sequences represent the reverse complement of the preferred antisense compounds shown in Tables 12 and 13. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 18 is the species in which each of the preferred target segments was found.

Example 33

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Targeting the Genomic sequence

In accordance with the present invention, another series of oligonucleotides were designed to target different regions of the human apolipoprotein B RNA, using published sequence (the complement of nucleotides 39835 to 83279 of the sequence with GenBank accession number NT_022227.9, representing a genomic sequence, incorporated herein as SEQ ID NO: 334). The oligonucleotides are shown in Table 14. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 14 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine

residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 14

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB	SEQ ID NO
301049	intron: exon junction	334	904	TCTGTAAGACAGGAGAAAGA	41	335
301050	intron: exon junction	334	913	ATTTCCTCTTCTGTAAGACA	22	336
301051	exon: intron junction	334	952	GATGCCTTACTTGGACAGAC	27	337
301052	intron	334	1945	AGAAATAGCTCTCCCAAGGA	13	338
301053	intron: exon junction	334	1988	GTCGCATCTTCTAACGTGGG	45	339
301054	exon: intron junction	334	2104	TCCTCCATACCTTGCAGTTG	0	340
301055	intron	334	2722	TGGCTCATGTCTACCATATT	49	341
301056	intron	334	2791	CAGTTGAAATGCAGCTAATG	35	342
301057	intron	334	3045	TGCAGACTAGGAGTGAAAGT	30	343
301058	intron	334	3117	AGGAGGATGTCCTTTTATTG	27	344
301059	intron	334	3290	ATCAGAGCACCAAAGGGAAT	12	345
301060	intron: exon junction	334	3381	CCAGCTCAACCTGAGAATTC	17	346
301061	exon: intron junction	334	3527	CATGACTTACCTGGACATGG	52	347
301062	intron	334	3566	CCTCAGCGGACACACACACA	21	348
301063	intron	334	3603	GTCACATCCGTGCCTGGTGC	41	349
301064	intron	334	3864	CAGTGCCTCTGGGACCCCAC	60	350
301065	intron	334	3990	AGCTGCAGTGGCCGATCAGC	50	351
301066	intron	334	4251	GACCTCCCCAGCCACGTGGA	61	352
301067	intron	334	4853	TCTGATCACCATACATTACA	45	353

301068	intron	334	5023	ATTTCCCACTGGGTACTCTC	44	354
301069	intron	334	5055	GGCTGAAGCCCATGCTGACT	44	355
301070	intron	334	5091	GTTGGACAGTCATTCTTTTG	38	356
301071	intron	334	5096	CACTTGTTGGACAGTCATTC	48	357
301072	intron	334	5301	ATTTTAAATTACAGTAGATA	43	358
301073	intron	334	5780	CTGTTCTCCACCCATATCAG	37	359
301074	intron: exon junction	334	6353	GAGCTCATACCTGTCCCAGA	75	360
301075	intron	334	6534	TTCAAGGGCCACTGCTATCA	52	361
301076	intron	334	6641	CCAGTATTTCACGCCAATCC	36	362
301077	intron	334	6661	GGCAGGAGGAACCTCGGGCA	55	363
301078	intron	334	6721	TTTTAAAATTAGACCCAACC	22	364
301079	intron	334	6727	TGACTGTTTTAAAATTAGAC	20	365
301080	intron	334	6788	CCCAGCAAACACAGGTGAAG	25	366
301081	intron	334	7059	GAGTGTGGTCTTGCTAGTGC	46	367
301082	intron	334	7066	CTATGCAGAGTGTGGTCTTG	41	368
301083	intron	334	7189	AGAAGATGCAACCACATGTA	29	369
301084	intron: exon junction	334	7209	ACACGGTATCCTATGGAGGA	49	370
301085	exon: intron junction	334	7365	TGGGACTTACCATGCCTTTG	11	371
301086	intron	334	7702	GGTTTTGCTGCCCTACATCC	30	372
301087	intron	334	7736	ACAAGGAGTCCTTGTGCAGA	40	373
301088	intron	334	8006	ATGTTCACTGAGACAGGCTG	41	374
301089	intron	334	8215	GAAGGTCCATGGTTCATCTG	0	375
301090	intron	334	8239	ATTAGACTGGAAGCATCCTG	39	376
301091	intron	334	8738	GAGATTGGAGACGAGCATTT	35	377
301092	exon: intron junction	334	8881	CATGACCTACTTGTAGGAGA	22	378
301093	intron	334	9208	TGGATTTGGATACACAAGTT	42	379
301094	intron	334	9244	ACTCAATATATATTCATTGA	22	380
301095	intron	334	9545	CAAGGAAGCACACCATGTCA	38	381
301096	intron: exon junction	334	9563	ATACTTATTCCTGGTAACCA	24	382
301097	intron	334	9770	GGTAGCCAGAACACCAGTGT	50	383
301098	intron	334	9776	ACTAGAGGTAGCCAGAACAC	34	384
301099	intron	334	10149	ACCACCTGACATCACAGGTT	24	385
301100	intron	334	10341	TACTGTGACCTATGCCAGGA	55	386
301101	intron	334	10467	GGAGGTGCTACTGTTGACAT	42	387
301102	intron	334	10522	TCCAGACTTGTCTGAGTCTA	47	388
301103	intron	334	10547	TCTAAGAGGTAGAGCTAAAG	7	389
301104	intron	334	10587	CCAGAGATGAGCAACTTAGG	38	390
301105	intron	334	10675	GGCCATGTAAATTGCTCATC	7	391
301106	intron	334	10831	AAAGAAACTATCCTGTATTC	12	392
301107	intron: exon junction	334	10946	TTCTTAGTACCTGGAAGATG	23	393

301108	exon: intron junction	334	11166	CATTAGATACCTGGACACCT	29	394
301109	intron	334	11337	GTTTCATGGAACTCAGCGCA	44	395
301110	intron	334	11457	CTGGAGAGCACCTGCAATAG	35	396
301111	intron	334	11521	TGAAGGGTAGAGAAATCATA	9	397
301112	exon: intron junction	334	12111	GGAAACTCACTTGTTGACCG	25	398
301113	intron	334	12155	AGGTGCAAGATGTTCCTCTG	46	399
301114	intron	334	12162	TGCACAGAGGTGCAAGATGT	16	400
301115	intron	334	12221	CACAAGAGTAAGGAGCAGAG	39	401
301116	intron	334	12987	GATGGATGGTGAGAAATTAC	33	402
301117	intron	334	13025	TAGACAATTGAGACTCAGAA	39	403
301118	intron	334	13057	ATGTGCACACAAGGACATAG	33	404
301119	intron	334	13634	ACATACAAATGGCAATAGGC	33	405
301120	intron	334	13673	TAGGCAAAGGACATGAATAG	30	406
301121	coding	334	14448	TTATGATAGCTACAGAATAA	29	407
301122	exon: intron junction	334	14567	CTGAGATTACCCGCAGAATC	32	408
301123	intron	334	14587	GATGTATGTCATATAAAAGA	26	409
301124	intron: exon junction	334	14680	TTTCCAATGACCTGCATTGA	48	410
301125	intron	334	15444	AGGGATGGTCAATCTGGTAG	57	411
301126	intron	334	15562	GGCTAATAAATAGGGTAGTT	22	412
301127	intron	334	15757	TCCTAGAGCACTATCAAGTA	41	413
301128	intron: exon junction	334	15926	CCTCCTGGTCCTGCAGTCAA	56	414
301129	intron	334	16245	CATTTGCACAAGTGTTTGTT	35	415
301130	intron	334	16363	CTGACACACCATGTTATTAT	10	416
301131	intron: exon junction	334	16399	CTTTTTCAGACTAGATAAGA	0	417
301132	exon: intron junction	334	16637	TCACACTTACCTCGATGAGG	29	418
301133	intron	334	17471	AAGAAAATGGCATCAGGTTT	13	419
301134	intron: exon junction	334	17500	CCAAGCCAATCTGAGAAAGA	25	420
301135	exon: intron junction	334	17677	AAATACACACCTGCTCATGT	20	421
301136	exon: intron junction	334	17683	CTTCACAAATACACACCTGC	20	422
301137	intron	334	18519	AGTGGAAGTTTGGTCTCATT	41	423
301138	intron	334	18532	TTGCTAGCTTCAAAGTGGAA	44	424
301139	intron	334	18586	TCAAGAATAAGCTCCAGATC	41	425
301140	intron	334	18697	GCATACAAGTCACATGAGGT	34	426

301141	intron	334	18969	TACAAGGTGTTTCTTAAGAA	38	427
301142	intron	334	19250	ATGCAGCCAGGATGGGCCTA	54	428
301143	intron: exon junction	334	19340	TTACCATATCCTGAGAGTTT	55	429
301144	intron	334	19802	GCAAAGGTAGAGGAAGGTAT	32	430
301145	intron	334	19813	AAGGACCTTCAGCAAAGGTA	36	431
301146	intron	334	20253	CATAGGAGTACATTTATATA	23	432
301147	intron	334	20398	ATTATGATAAAATCAATTTT	19	433
301148	intron	334	20567	AGAAATTTCACTAGATAGAT	31	434
301149	intron	334	20647	AGCATATTTTGATGAGCTGA	44	435
301150	intron	334	20660	GAAAGGAAGGACTAGCATAT	39	436
301151	intron: exon junction	334	20772	CCTCTCCAATCTGTAGACCC	28	437
301152	intron	334	21316	CTGGATAACTCAGACCTTTG	40	438
301153	intron	334	21407	AGTCAGAAAACAACCTATTC	11	439
301154	intron: exon junction	334	21422	CAGCCTGCATCTATAAGTCA	31	440
301155	exon: intron junction	334	21634	AAAGAATTACCCTCCACTGA	33	441
301156	intron	334	21664	TCTTTCAAACTGGCTAGGCA	39	442
301157	intron	334	21700	GCCTGGCAAAATTCTGCAGG	37	443
301158	intron	334	22032	CTACCTCAAATCAATATGTT	28	444
301159	intron	334	22048	TGCTTTACCTACCTAGCTAC	36	445
301160	intron	334	22551	ACCTTGTGTGTCTCACTCAA	49	446
301161	intron	334	22694	ATGCATTCCCTGACTAGCAC	34	447
301162	intron	334	22866	CATCTCTGAGCCCCTTACCA	24	448
301163	intron	334	22903	GCTGGGCATGCTCTCTCCCC	51	449
301164	intron	334	22912	GCTTTCGCAGCTGGGCATGC	55	450
301165	intron	334	23137	ACTCCTTTCTATACCTGGCT	47	451
301166	intron	334	23170	ATTCTGCCTCTTAGAAAGTT	38	452
301167	intron	334	23402	CCAAGCCTCTTTACTGGGCT	29	453
301168	intron	334	23882	CACTCATGACCAGACTAAGA	35	454
301169	intron	334	23911	ACCTCCCAGAAGCCTTCCAT	22	455
301170	intron	334	24184	TTCATATGAAATCTCCTACT	40	456
301171	intron	334	24425	TATTTAATTTACTGAGAAAC	7	457
301172	intron: exon junction	334	24559	TAATGTGTTGCTGGTGAAGA	35	458
301173	exon: intron junction	334	24742	CATCTCTAACCTGGTGTCCC	21	459
301174	intron	334	24800	GTGCCATGCTAGGTGGCCAT	37	460
301175	intron	334	24957	AGCAAATTGGGATCTGTGCT	29	461
301176	intron	334	24991	TCTGGAGGCTCAGAAACATG	57	462
301177	intron	334	25067	TGAAGACAGGGAGCCACCTA	40	463
301178	intron	334	25152	AGGATTCCCAAGACTTTGGA	38	464
301179	intron: exon	334	25351	CAGCTCTAATCTAAAGACAT	22	465

	junction					
301180	exon: intron junction	334	25473	GAATACTCACCTTCTGCTTG	6	466
301181	intron	334	26047	ATCTCTCTGTCCTCATCTTC	28	467
301182	intron	334	26749	CCAACTCCCCCTTTCTTTGT	37	468
301183	intron	334	26841	TCTGGGCCAGGAAGACACGA	68	469
301184	intron	334	27210	TATTGTGTGCTGGGCACTGC	52	470
301185	intron: exon junction	334	27815	TGCTTCGCACCTGGACGAGT	51	471
301186	exon: intron junction	334	28026	CCTTCTTTACCTTAGGTGGC	37	472
301187	intron	334	28145	GCTCTCTCTGCCACTCTGAT	47	473
301188	intron	334	28769	AACTTCTAAAGCCAACATTC	27	474
301189	intron: exon junction	334	28919	TGTGTCACAACTATGGTAAA	63	475
301190	exon: intron junction	334	29095	AGACACATACCATAATGCCA	22	476
301191	intron: exon junction	334	29204	TTCTCTTCATCTGAAAATAC	21	477
301192	intron	334	29440	TGAGGATGTAATTAGCACTT	27	478
301193	intron: exon junction	334	29871	AGCTCATTGCCTACAAAATG	31	479
301194	intron	334	30181	GTTCTCATGTTTACTAATGC	40	480
301195	intron	334	30465	GAATTGAGACAACTTGATTT	26	481
301196	intron: exon junction	334	30931	CCGGCCATCGCTGAAATGAA	54	482
301197	exon: intron junction	334	31305	CATAGCTCACCTTGCACATT	28	483
301198	intron	334	31325	CGGTGCACCCTTTACCTGAG	28	484
301199	intron: exon junction	334	31813	TCTCCAGATCCTAACATAAA	19	485
301200	intron	334	39562	TTGAATGACACTAGATTTTC	37	486
301201	intron	334	39591	AAAATCCATTTTCTTTAAAG	12	487
301202	intron	334	39654	CAGCTCACACTTATTTTAAA	7	488
301203	intron: exon junction	334	39789	GTTCCCAAAACTGTATAGGA	36	489
301204	exon: intron junction	334	39904	AGCTCCATACTGAAGTCCTT	37	490
301205	intron	334	39916	CAATTCAATAAAAGCTCCAT	31	491
301206	intron	334	39938	GTTTTCAAAAGGTATAAGGT	28	492
301207	intron: exon	334	40012	TTCCCATTCCCTGAAAGCAG	13	493

	junction					
301208	exon: intron junction	334	40196	TGGTATTTACCTGAGGGCTG	21	494
301209	intron	334	40412	ATAAATAATAGTGCTGATGG	39	495
301210	intron	334	40483	CTATGGCTGAGCTTGCCTAT	33	496
301211	intron	334	40505	CTCTCTGAAAAATATACCCT	17	497
301212	intron	334	40576	TTGATGTATCTCATCTAGCA	41	498
301213	intron	334	40658	TAGAACCATGTTTGGTCTTC	35	499
301214	intron	334	40935	TTTCTCTTTATCACATGCCC	29	500
301215	intron	334	41066	TATAGTACACTAAAACTTCA	1	501
301216	intron: exon junction	334	41130	CTGGAGAGGACTAAACAGAG	49	502

As shown in Table 14, SEQ ID Nos 335, 339, 341, 342, 343, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 367, 368, 370, 372, 373, 374, 376, 377, 379, 381, 383, 384, 386, 387, 388, 390, 395, 396, 399, 401, 402, 403, 404, 405, 406, 408, 410, 411, 413, 414, 415, 423, 424, 425, 426, 427, 428, 429, 430, 431, 434, 435, 436, 438, 440, 441, 442, 443, 445, 446, 447, 449, 450, 451, 452, 454, 456, 458, 460, 462, 463, 464, 468, 469, 470, 471, 472, 473, 475, 479, 480, 482, 486, 489, 490, 491, 495, 496, 498, 499, and 502 demonstrated at least 30% inhibition of human apolipoprotein B expression in this assay and are therefore preferred. The target regions to which these preferred sequences are complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 18. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 14. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide

binds. Also shown in Table 18 is the species in which each of the preferred target segments was found.

Example 34

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Targeting GenBank accession number AI249040.1

In accordance with the present invention, another series of oligonucleotides were designed to target different regions of the human apolipoprotein B RNA, using published sequence (the complement of the sequence with GenBank accession number AI249040.1, incorporated herein as SEQ ID NO: 503). The oligonucleotides are shown in Table 15. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 15 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 15

Inhibition of human apolipoprotein B mRNA levels by

chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	REGION	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB	SEQ ID NO
301218	3'UTR	503	484	ACATTTTATCAATGCCCTCG	23	504
301219	3'UTR	503	490	GCCAGAACATTTTATCAATG	35	505
301220	3'UTR	503	504	AGAGGTTTTGCTGTGCCAGA	51	506
301221	3'UTR	503	506	CTAGAGGTTTTGCTGTGCCA	61	507
301222	3'UTR	503	507	TCTAGAGGTTTTGCTGTGCC	14	508
301223	3'UTR	503	522	AATCACACTATGTGTTCTAG	26	509
301224	3'UTR	503	523	AAATCACACTATGTGTTCTA	33	510
301225	3'UTR	503	524	TAAATCACACTATGTGTTCT	3	511
301226	3'UTR	503	526	CTTAAATCACACTATGTGTT	39	512
301227	3'UTR	503	536	TATTCTGTTACTTAAATCAC	23	513

As shown in Table 15, SEQ ID Nos 505, 506, 507, 510, and 512 demonstrated at least 30% inhibition of human apolipoprotein B expression in this assay and are therefore preferred. The target regions to which these preferred sequences are complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 18. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 15. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 18 is the species in which each of the preferred target segments was found.

Example 35

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Variation in position of the gap

In accordance with the present invention, a series of antisense compounds were designed to target different

regions of the human apolipoprotein B RNA, using published sequences (GenBank accession number NM_000384.1, incorporated herein as SEQ ID NO: 3). The compounds are shown in Table 16. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the compound binds. All compounds in Table 13 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length. The "gap" region consists of 2'-deoxynucleotides, which is flanked on one or both sides (5' and 3' directions) by "wings" composed of 2'-methoxyethyl (2'-MOE)nucleotides. The number of 2'-MOE nucleotides on either side of the gap varies such that the total number of 2'-MOE nucleotides always equals 10 and the total length of the chimeric oligonucleotide is 20 nucleotides. The exact structure of each oligonucleotide is designated in Table 16 as the "gap structure" and the 2'-deoxynucleotides are in bold type. A designation of 8-10-2, for instance, indicates that the first (5'-most) 8 nucleotides and the last (3'-most) 2 nucleotides are 2'-MOE nucleotides and the 10 nucleotides in the gap are 2'-deoxynucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from three experiments in which HepG2 cells were treated with the antisense oligonucleotides of the present invention at a dose of 50 nM and 150 nM. If present, "N.D." indicates "no data".

Table 16

Inhibition of human apolipoprotein B mRNA levels by

chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a variable deoxy gap

ISIS #	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB 150 nM	% INHIB 50 nM	gap structure	SEQ ID NO
308631	3	5589	AGGTTACCAGCCACATGCAG	94	74	0-10-10	224
308632	3	3249	GCCTCAGTCTGCTTCGCACC	97	41	0-10-10	247
308634	3	5589	AGGTTACCAGCCACATGCAG	67	45	10-10-0	224
308635	3	3249	GCCTCAGTCTGCTTCGCACC	93	69	10-10-0	247
308637	3	5589	AGGTTACCAGCCACATGCAG	95	79	1-10-9	224
308638	3	3249	GCCTCAGTCTGCTTCGCACC	94	91	1-10-9	247
308640	3	5589	AGGTTACCAGCCACATGCAG	96	76	2-10-8	224
308641	3	3249	GCCTCAGTCTGCTTCGCACC	89	77	2-10-8	247
308643	3	5589	AGGTTACCAGCCACATGCAG	96	56	3-10-7	224
308644	3	3249	GCCTCAGTCTGCTTCGCACC	93	71	3-10-7	247
308646	3	5589	AGGTTACCAGCCACATGCAG	76	50	4-10-6	224
308647	3	3249	GCCTCAGTCTGCTTCGCACC	86	53	4-10-6	247
308649	3	5589	AGGTTACCAGCCACATGCAG	91	68	6-10-4	224
308650	3	3249	GCCTCAGTCTGCTTCGCACC	94	74	6-10-4	247
308652	3	5589	AGGTTACCAGCCACATGCAG	95	73	7-10-3	224
308653	3	3249	GCCTCAGTCTGCTTCGCACC	89	73	7-10-3	247
308655	3	5589	AGGTTACCAGCCACATGCAG	83	84	8-10-2	224
308656	3	3249	GCCTCAGTCTGCTTCGCACC	97	37	8-10-2	247
308658	3	5589	AGGTTACCAGCCACATGCAG	78	86	9-10-1	224
308659	3	3249	GCCTCAGTCTGCTTCGCACC	93	70	9-10-1	247
308660	3	3254	TGGTAGCCTCAGTCTGCTTC	92	72	2-10-8	514
308662	3	3254	TGGTAGCCTCAGTCTGCTTC	83	76	8-10-2	514

As shown in Table 16, SEQ ID Nos 224, 247, and 514 demonstrated at least 30% inhibition of human apolipoprotein B expression in this assay at both doses. These data suggest that the oligonucleotides are effective with a number of variations in the gap placement. The target regions to which these preferred sequences are complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the present invention. These preferred target segments are shown in Table 18. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 16. "Target site" indicates the first (5'-

most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 18 is the species in which each of the preferred target segments was found.

Example 36

Antisense inhibition of human apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Variation in position of the gap of SEQ ID Nos: 319 and 515

In accordance with the present invention, a series of antisense compounds were designed based on SEQ ID Nos 319 and 515, with variations in the gap structure. The compounds are shown in Table 17. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the compound binds. All compounds in Table 17 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length. The "gap" region consists of 2'-deoxynucleotides, which is flanked on one or both sides (5' and 3' directions) by "wings" composed of 2'-methoxyethyl (2'-MOE) nucleotides. The number of 2'-MOE nucleotides on either side of the gap varies such that the total number of 2'-MOE nucleotides always equals 10 and the total length of the chimeric oligonucleotide is 20 nucleotides. The exact structure of each oligonucleotide is designated in Table 17 as the "gap structure" and the 2'-deoxynucleotides are in bold type. A designation of 8-10-2, for instance, indicates that the first (5'-most) 8 nucleotides and the last (3'-most) 2 nucleotides are 2'-MOE nucleotides and the 10 nucleotides in the gap are 2'-deoxynucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine

residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein C-III mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from three experiments in which HepG2 cells were treated with the antisense oligonucleotides of the present invention at a dose of 50 nM and 150 nM. If present, "N.D." indicates "no data".

Table 17

Inhibition of human apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a variable deoxy gap

ISIS #	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	% INHIB 150 nM	% INHIB 50 nM	gap structure	SEQ ID NO
308630	318	3121	GCCTCAGTCTGCTTCGCGCC	89	69	0-10-10	319
308633	318	3121	GCCTCAGTCTGCTTCGCGCC	83	66	10-10-0	319
308636	318	3121	GCCTCAGTCTGCTTCGCGCC	91	81	1-10-9	319
308639	318	3121	GCCTCAGTCTGCTTCGCGCC	94	86	2-10-8	319
308642	318	3121	GCCTCAGTCTGCTTCGCGCC	95	85	3-10-7	319
308645	318	3121	GCCTCAGTCTGCTTCGCGCC	98	57	4-10-6	319
308648	318	3121	GCCTCAGTCTGCTTCGCGCC	89	78	6-10-4	319
308651	318	3121	GCCTCAGTCTGCTTCGCGCC	88	87	7-10-3	319
308654	318	3121	GCCTCAGTCTGCTTCGCGCC	90	81	8-10-2	319
308657	318	3121	GCCTCAGTCTGCTTCGCGCC	78	61	9-10-1	319
308661	318	3116	AGTCTGCTTCGCGCCTTCTG	91	70	2-10-8	515
308663	318	3116	AGTCTGCTTCGCGCCTTCTG	84	44	8-10-2	515

As shown in Table 17, SEQ ID Nos 319 and 515 demonstrated at least 44% inhibition of human apolipoprotein B expression in this assay for either dose. These data suggest that the compounds are effective with a number of variations in gap placement. The target regions to which these preferred sequences are complementary are herein referred to as "preferred target segments" and are therefore preferred for targeting by compounds of the

present invention. These preferred target segments are shown in Table 18. The sequences represent the reverse complement of the preferred antisense compounds shown in Table 17. "Target site" indicates the first (5'-most) nucleotide number on the particular target nucleic acid to which the oligonucleotide binds. Also shown in Table 18 is the species in which each of the preferred target segments was found.

Table 18

Sequence and position of preferred target segments identified in apolipoprotein B.

SITE ID	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	REV COMP OF SEQ ID NO	ACTIVE IN	SEQ ID NO
187342	3	199	GCGCCAGGGCCGAAGAGGAA	124	*H. sapiens*	516
187346	3	509	CAGGTATGAGCTCAAGCTGG	128	*H. sapiens*	517
187347	3	584	CATCCTGAACATCAAGAGGG	129	*H. sapiens*	518
187350	3	756	GGGCAGTGTGATCGCTTCAA	132	*H. sapiens*	519
187351	3	799	CACTTGCTCTCATCAAAGGC	133	*H. sapiens*	520
187352	3	869	CACACTGGACGCTAAGAGGA	134	*H. sapiens*	521
187356	3	1459	CGCTGAGCCACGCGGTCAAC	138	*H. sapiens*	522
187358	3	1859	TGTCCAAATTCTACCATGGG	140	*H. sapiens*	523
187359	3	2179	CAGCTGACCTCATCGAGATT	141	*H. sapiens*	524
187360	3	2299	GTCAAGTTCCTGATGGTGTC	142	*H. sapiens*	525
187362	3	2518	AGCTGCTTCTGATGGGTGCC	144	*H. sapiens*	526
187363	3	2789	GGGCATCATCATTCCGGACT	145	*H. sapiens*	527
187365	3	3100	CCTACTATCCGCTGACCGGG	147	*H. sapiens*	528
187367	3	3449	GGGCCACCTAAGTTGTGACA	148	*H. sapiens*	529
187368	3	3919	AGAACATGGGATTGCCAGAC	149	*H. sapiens*	530
187369	3	4089	CTCCACTTCAAGTCTGTGGG	150	*H. sapiens*	531
187371	3	5146	CAGAGCTTGGCCTCTCTGGG	152	*H. sapiens*	532
187372	3	5189	TGGCCGCTTCAGGGAACACA	153	*H. sapiens*	533
187374	3	6049	CAGCTGAGCAGACAGGCACC	155	*H. sapiens*	534
187375	3	6520	GGGAGAGACAAGTTTCACAT	156	*H. sapiens*	535
187377	3	6859	GTACTGCATCCTGGATTCAA	158	*H. sapiens*	536
187378	3	7459	GTGAGGTGACTCAGAGACTC	159	*H. sapiens*	537
187379	3	7819	TTGCAGAGCAATATTCTATC	160	*H. sapiens*	538
187380	3	7861	AAGCATTGGTAGAGCAAGGG	161	*H. sapiens*	539
187383	3	8589	CCGCTGGCTCTGAAGGAGTC	163	*H. sapiens*	540
187385	3	8829	TCTAGTCAGGCTGACCTGCG	165	*H. sapiens*	541
187387	3	9119	GGGCCACAGTGTTCTAACTG	166	*H. sapiens*	542

187388	3	10159	AATCAAGTGTCATCACACTG	167	*H. sapiens*	543
187390	3	10349	GGGTAGTCATAACAGTACTG	169	*H. sapiens*	544
187391	3	10699	AGAGCACACGGTCTTCAGTG	170	*H. sapiens*	545
187393	3	10839	TTACAGCTAGAGGGCCTCTT	172	*H. sapiens*	546
187398	3	12149	CACCGTGGGCATGGATATGG	176	*H. sapiens*	547
187399	3	12265	GGGAATCTGATGAGGAAACT	177	*H. sapiens*	548
187400	3	12380	TGTCAACAAGTACCACTGGG	178	*H. sapiens*	549
187403	3	12749	ACCTGGGATATACACTAGGG	181	*H. sapiens*	550
187406	3	13299	CCAAGTATAGTTGGCTGGAC	183	*H. sapiens*	551
187407	3	13779	TACATGAAGCTTGCTCCAGG	184	*H. sapiens*	552
197724	3	229	ATGTCAGCCTGGTCTGTCCA	185	*H. sapiens*	553
197725	3	269	GCACCTCCGGAAGTACACAT	186	*H. sapiens*	554
197726	3	389	CTGCAGCTTCATCCTGAAGA	187	*H. sapiens*	555
197727	3	449	TGAGGGCAAAGCCTTGCTGA	188	*H. sapiens*	556
197728	3	529	CCATTCCAGAAGGGAAGCAG	189	*H. sapiens*	557
197729	3	709	CGAGGAAGGGCAATGTGGCA	190	*H. sapiens*	558
197730	3	829	CCTTGTCAACTCTGATCAGC	191	*H. sapiens*	559
197731	3	849	AGCAGCCAGTCCTGTCAGTA	192	*H. sapiens*	560
197732	3	889	AGCATGTGGCAGAAGCCATC	193	*H. sapiens*	561
197733	3	1059	GAGAGCACCAAATCCACATC	194	*H. sapiens*	562
197734	3	1199	CCTCAGTGATGAAGCAGTCA	195	*H. sapiens*	563
197735	3	1349	GATAGATGTGGTCACCTACC	196	*H. sapiens*	564
197736	3	1390	CCTCAGCACAGCAGCTGCGA	197	*H. sapiens*	565
197737	3	1589	GATTCTGCGGGTCATTGGAA	198	*H. sapiens*	566
197738	3	1678	CAAAGCCATCACTGATGATC	199	*H. sapiens*	567
197739	3	1699	AGAAAGCTGCCATCCAGGCT	200	*H. sapiens*	568
197740	3	1749	CAGGAGGTTCTTCTTCAGAC	201	*H. sapiens*	569
197741	3	1829	GAGTCCTTCACAGGCAGATA	202	*H. sapiens*	570
197742	3	1919	TGCCAATATCTTGAACTCAG	203	*H. sapiens*	571
197743	3	2189	CATCGAGATTGGCTTGGAAG	204	*H. sapiens*	572
197744	3	2649	GGAGCTGGATTACAGTTGCA	205	*H. sapiens*	573
197745	3	2729	CAACATGCAGGCTGAACTGG	206	*H. sapiens*	574
197746	3	2949	ACATTACATTTGGTCTCTAC	207	*H. sapiens*	575
197747	3	3059	CTCAGGCGCTTACTCCAACG	208	*H. sapiens*	576
197748	3	3118	GGGACACCAGATTAGAGCTG	209	*H. sapiens*	577
197749	3	3189	GAGCTCCAGAGAGAGGACAG	210	*H. sapiens*	578
197750	3	3289	ATCGGCAGAGTATGACCTTG	211	*H. sapiens*	579
197751	3	3488	CAAGGGTGTTATTTCCATAC	212	*H. sapiens*	580
197752	3	3579	GACTCATCTGCTACAGCTTA	213	*H. sapiens*	581
197753	3	4039	GCAAATCCTCCAGAGATCTA	214	*H. sapiens*	582
197754	3	4180	CTCTCCTGGGTGTTCTAGAC	215	*H. sapiens*	583
197755	3	4299	ATGAAGGCTGACTCTGTGGT	216	*H. sapiens*	584
197756	3	4511	GGGACCACAGATGTCTGCTT	217	*H. sapiens*	585
197757	3	4660	CTGGCCGGCTCAATGGAGAG	218	*H. sapiens*	586
197758	3	4919	GCTGCGTTCTGAATATCAGG	219	*H. sapiens*	587
197759	3	5009	TGCTGACATCTTAGGCACTG	220	*H. sapiens*	588
197760	3	5109	AAGTGTAGTCTCCTGGTGCT	221	*H. sapiens*	589
197761	3	5212	CAAAATTCAGTCTGGATGGG	222	*H. sapiens*	590

197762	3	5562	GGGAAACTACGGCTAGAACC	223	*H. sapiens*	591
197763	3	5589	CTGCATGTGGCTGGTAACCT	224	*H. sapiens*	592
197764	3	5839	CCATGACCATCGATGCACAT	225	*H. sapiens*	593
197765	3	5869	ATGGGAAACTCGCTCTCTGG	226	*H. sapiens*	594
197766	3	5979	AGTCATCATCTCGTGTCTAG	227	*H. sapiens*	595
197767	3	6099	GAATACAGCCAGGACTTGGA	228	*H. sapiens*	596
197768	3	6144	GGCGTGGAGCTTACTGGACG	229	*H. sapiens*	597
197769	3	6249	GAGATGAGAGATGCCGTTGA	230	*H. sapiens*	598
197770	3	6759	AGTCTTGATGAGCACTATCA	231	*H. sapiens*	599
197771	3	6889	CTAAGTACCAAATCAGAATC	232	*H. sapiens*	600
197772	3	7149	GTCCATGAGTTAATCGAGAG	233	*H. sapiens*	601
197773	3	7549	AGGCCACAGTTGCAGTGTAT	234	*H. sapiens*	602
197774	3	7779	TCTGATTGGTGGACTCTTGC	235	*H. sapiens*	603
197775	3	7929	GAAGTCAGTCTTCAGGCTCT	236	*H. sapiens*	604
197776	3	8929	CCAGATTCTCAGATGAGGGA	237	*H. sapiens*	605
197778	3	10240	CATCTGTCATTGATGCACTG	238	*H. sapiens*	606
197779	3	10619	AGGAGATGTCAAGGGTTCGG	239	*H. sapiens*	607
197780	3	10659	GGAACTATTGCTAGTGAGGC	240	*H. sapiens*	608
197781	3	10899	CTCTCTCCATGGCAAATGTC	241	*H. sapiens*	609
197783	3	11979	CACCGTGACTTCAGTGCAGA	243	*H. sapiens*	610
197784	3	12249	ACTGAGTTGAGGGTCCGGGA	244	*H. sapiens*	611
197786	3	13958	CACATATGAACTGGACCTGC	245	*H. sapiens*	612
197787	3	14008	TCTGAACTCAGAAGGATGGC	246	*H. sapiens*	613
216825	3	3249	GGTGCGAAGCAGACTGAGGC	247	*H. sapiens*	614
216826	3	3	TCCCACCGGGACCTGCGGGG	248	*H. sapiens*	615
216827	3	6	CACCGGGACCTGCGGGGCTG	249	*H. sapiens*	616
216828	3	23	CTGAGTGCCCTTCTCGGTTG	250	*H. sapiens*	617
216829	3	35	CTCGGTTGCTGCCGCTGAGG	251	*H. sapiens*	618
216830	3	36	TCGGTTGCTGCCGCTGAGGA	252	*H. sapiens*	619
216831	3	37	CGGTTGCTGCCGCTGAGGAG	253	*H. sapiens*	620
216832	3	39	GTTGCTGCCGCTGAGGAGCC	254	*H. sapiens*	621
216833	3	43	CTGCCGCTGAGGAGCCCGCC	255	*H. sapiens*	622
216834	3	116	ACCGCAGCTGGCGATGGACC	256	*H. sapiens*	623
216835	3	120	CAGCTGGCGATGGACCCGCC	257	*H. sapiens*	624
216836	3	13800	GAACTTACTATCATCCTCTA	258	*H. sapiens*	625
216838	3	13854	TCCAATTGAACTTTCACATA	260	*H. sapiens*	626
216839	3	13882	AAAATTCAAACTGCCTATAT	261	*H. sapiens*	627
216840	3	13903	GATAAAACCATACAGTGAGC	262	*H. sapiens*	628
216841	3	13904	ATAAAACCATACAGTGAGCC	263	*H. sapiens*	629
216842	3	13908	AACCATACAGTGAGCCAGCC	264	*H. sapiens*	630
216843	3	13909	ACCATACAGTGAGCCAGCCT	265	*H. sapiens*	631
216844	3	13910	CCATACAGTGAGCCAGCCTT	266	*H. sapiens*	632
216845	3	13917	GTGAGCCAGCCTTGCAGTAG	267	*H. sapiens*	633
216846	3	13922	CCAGCCTTGCAGTAGGCAGT	268	*H. sapiens*	634
216847	3	13934	TAGGCAGTAGACTATAAGCA	269	*H. sapiens*	635
216848	3	13937	GCAGTAGACTATAAGCAGAA	270	*H. sapiens*	636
216849	3	13964	TGAACTGGACCTGCACCAAA	271	*H. sapiens*	637
216850	3	13968	CTGGACCTGCACCAAAGCTG	272	*H. sapiens*	638

216851	3	13970	GGACCTGCACCAAAGCTGGC	273	*H. sapiens*	639
216852	3	13974	CTGCACCAAAGCTGGCACCA	274	*H. sapiens*	640
216853	3	13978	ACCAAAGCTGGCACCAGGGC	275	*H. sapiens*	641
216854	3	13997	CTCGGAAGGTCTCTGAACTC	276	*H. sapiens*	642
216855	3	14012	AACTCAGAAGGATGGCATTT	277	*H. sapiens*	643
216856	3	14014	CTCAGAAGGATGGCATTTTT	278	*H. sapiens*	644
216857	3	14049	ATCAGGATCTGAGTTATTTT	279	*H. sapiens*	645
216858	3	14052	AGGATCTGAGTTATTTTGCT	280	*H. sapiens*	646
216859	3	14057	CTGAGTTATTTTGCTAAACT	281	*H. sapiens*	647
216860	3	14064	ATTTTGCTAAACTTGGGGGA	282	*H. sapiens*	648
216861	3	14071	TAAACTTGGGGGAGGAGGAA	283	*H. sapiens*	649
217030	3	14087	GGAACAAATAAATGGAGTCT	284	*H. sapiens*	650
224316	3	3230	GTTTGTAACTCAAGCAGAAG	285	*H. sapiens*	651
224317	3	3232	TTGTAACTCAAGCAGAAGGT	286	*H. sapiens*	652
224318	3	3234	GTAACTCAAGCAGAAGGTGC	287	*H. sapiens*	653
224319	3	3236	AACTCAAGCAGAAGGTGCGA	288	*H. sapiens*	654
224320	3	3238	CTCAAGCAGAAGGTGCGAAG	289	*H. sapiens*	655
224321	3	3240	CAAGCAGAAGGTGCGAAGCA	290	*H. sapiens*	656
224322	3	3242	AGCAGAAGGTGCGAAGCAGA	291	*H. sapiens*	657
224323	3	3244	CAGAAGGTGCGAAGCAGACT	292	*H. sapiens*	658
224324	3	3246	GAAGGTGCGAAGCAGACTGA	293	*H. sapiens*	659
224325	3	3248	AGGTGCGAAGCAGACTGAGG	294	*H. sapiens*	660
224326	3	3250	GTGCGAAGCAGACTGAGGCT	295	*H. sapiens*	661
224327	3	3252	GCGAAGCAGACTGAGGCTAC	296	*H. sapiens*	662
224328	3	3254	GAAGCAGACTGAGGCTACCA	297	*H. sapiens*	663
224329	3	3256	AGCAGACTGAGGCTACCATG	298	*H. sapiens*	664
224330	3	3258	CAGACTGAGGCTACCATGAC	299	*H. sapiens*	665
224331	3	3260	GACTGAGGCTACCATGACAT	300	*H. sapiens*	666
224332	3	3262	CTGAGGCTACCATGACATTC	301	*H. sapiens*	667
224333	3	3264	GAGGCTACCATGACATTCAA	302	*H. sapiens*	668
224334	3	3266	GGCTACCATGACATTCAAAT	303	*H. sapiens*	669
224335	3	3268	CTACCATGACATTCAAATAT	304	*H. sapiens*	670
224336	3	5582	CCTGAAGCTGCATGTGGCTG	305	*H. sapiens*	671
224337	3	5584	TGAAGCTGCATGTGGCTGGT	306	*H. sapiens*	672
224338	3	5586	AAGCTGCATGTGGCTGGTAA	307	*H. sapiens*	673
224339	3	5588	GCTGCATGTGGCTGGTAACC	308	*H. sapiens*	674
224340	3	5590	TGCATGTGGCTGGTAACCTA	309	*H. sapiens*	675
224341	3	5592	CATGTGGCTGGTAACCTAAA	310	*H. sapiens*	676
224342	3	5594	TGTGGCTGGTAACCTAAAAG	311	*H. sapiens*	677
224343	3	5596	TGGCTGGTAACCTAAAAGGA	312	*H. sapiens*	678
224344	3	5598	GCTGGTAACCTAAAAGGAGC	313	*H. sapiens*	679
224345	3	5600	TGGTAACCTAAAAGGAGCCT	314	*H. sapiens*	680
224346	3	5602	GTAACCTAAAAGGAGCCTAC	315	*H. sapiens*	681
224347	3	5604	AACCTAAAAGGAGCCTACCA	316	*H. sapiens*	682
224348	3	5606	CCTAAAAGGAGCCTACCAAA	317	*H. sapiens*	683
187366	318	3121	GGCGCGAAGCAGACTGAGGC	319	*H. sapiens*	684
187404	318	12651	CACTATGTTCATGAGGGAGG	323	*H. sapiens*	685
197777	318	9851	CCATCATAGGTTCTGACGTC	324	*H. sapiens*	686

197785	318	12561	GAAGCTGATTGACTCACTCA	325	*H. sapiens*	687
224349	318	3104	TTGTAACTCAAGCAGAAGGC	326	*H. sapiens*	688
224350	318	3106	GTAACTCAAGCAGAAGGCGC	327	*H. sapiens*	689
224351	318	3108	AACTCAAGCAGAAGGCGCGA	328	*H. sapiens*	690
224352	318	3110	CTCAAGCAGAAGGCGCGAAG	329	*H. sapiens*	691
224353	318	3116	CAGAAGGCGCGAAGCAGACT	330	*H. sapiens*	692
224354	318	3118	GAAGGCGCGAAGCAGACTGA	331	*H. sapiens*	693
224355	318	3120	AGGCGCGAAGCAGACTGAGG	332	*H. sapiens*	694
224356	318	3122	GCGCGAAGCAGACTGAGGCT	333	*H. sapiens*	695
224328	3	3254	GAAGCAGACTGAGGCTACCA	514	*H. sapiens*	696
224353	318	3116	CAGAAGGCGCGAAGCAGACT	515	*H. sapiens*	697
216862	334	904	TCTTTCTCCTGTCTTACAGA	335	*H. sapiens*	698
216866	334	1988	CCCACGTTAGAAGATGCGAC	339	*H. sapiens*	699
216868	334	2722	AATATGGTAGACATGAGCCA	341	*H. sapiens*	700
216869	334	2791	CATTAGCTGCATTTCAACTG	342	*H. sapiens*	701
216870	334	3045	ACTTTCACTCCTAGTCTGCA	343	*H. sapiens*	702
216874	334	3527	CCATGTCCAGGTAAGTCATG	347	*H. sapiens*	703
216876	334	3603	GCACCAGGCACGGATGTGAC	349	*H. sapiens*	704
216877	334	3864	GTGGGGTCCCAGAGGCACTG	350	*H. sapiens*	705
216878	334	3990	GCTGATCGGCCACTGCAGCT	351	*H. sapiens*	706
216879	334	4251	TCCACGTGGCTGGGGAGGTC	352	*H. sapiens*	707
216880	334	4853	TGTAATGTATGGTGATCAGA	353	*H. sapiens*	708
216881	334	5023	GAGAGTACCCAGTGGGAAAT	354	*H. sapiens*	709
216882	334	5055	AGTCAGCATGGGCTTCAGCC	355	*H. sapiens*	710
216883	334	5091	CAAAAGAATGACTGTCCAAC	356	*H. sapiens*	711
216884	334	5096	GAATGACTGTCCAACAAGTG	357	*H. sapiens*	712
216885	334	5301	TATCTACTGTAATTTAAAAT	358	*H. sapiens*	713
216886	334	5780	CTGATATGGGTGGAGAACAG	359	*H. sapiens*	714
216887	334	6353	TCTGGGACAGGTATGAGCTC	360	*H. sapiens*	715
216888	334	6534	TGATAGCAGTGGCCCTTGAA	361	*H. sapiens*	716
216889	334	6641	GGATTGGCGTGAAATACTGG	362	*H. sapiens*	717
216890	334	6661	TGCCCGAGGTTCCTCCTGCC	363	*H. sapiens*	718
216894	334	7059	GCACTAGCAAGACCACACTC	367	*H. sapiens*	719
216895	334	7066	CAAGACCACACTCTGCATAG	368	*H. sapiens*	720
216897	334	7209	TCCTCCATAGGATACCGTGT	370	*H. sapiens*	721
216899	334	7702	GGATGTAGGGCAGCAAAACC	372	*H. sapiens*	722
216900	334	7736	TCTGCACAAGGACTCCTTGT	373	*H. sapiens*	723
216901	334	8006	CAGCCTGTCTCAGTGAACAT	374	*H. sapiens*	724
216903	334	8239	CAGGATGCTTCCAGTCTAAT	376	*H. sapiens*	725
216904	334	8738	AAATGCTCGTCTCCAATCTC	377	*H. sapiens*	726
216906	334	9208	AACTTGTGTATCCAAATCCA	379	*H. sapiens*	727
216908	334	9545	TGACATGGTGTGCTTCCTTG	381	*H. sapiens*	728
216910	334	9770	ACACTGGTGTTCTGGCTACC	383	*H. sapiens*	729
216911	334	9776	GTGTTCTGGCTACCTCTAGT	384	*H. sapiens*	730
216913	334	10341	TCCTGGCATAGGTCACAGTA	386	*H. sapiens*	731
216914	334	10467	ATGTCAACAGTAGCACCTCC	387	*H. sapiens*	732
216915	334	10522	TAGACTCAGACAAGTCTGGA	388	*H. sapiens*	733
216917	334	10587	CCTAAGTTGCTCATCTCTGG	390	*H. sapiens*	734

216922	334	11337	TGCGCTGAGTTCCATGAAAC	395	*H. sapiens*	735
216923	334	11457	CTATTGCAGGTGCTCTCCAG	396	*H. sapiens*	736
216926	334	12155	CAGAGGAACATCTTGCACCT	399	*H. sapiens*	737
216928	334	12221	CTCTGCTCCTTACTCTTGTG	401	*H. sapiens*	738
216929	334	12987	GTAATTTCTCACCATCCATC	402	*H. sapiens*	739
216930	334	13025	TTCTGAGTCTCAATTGTCTA	403	*H. sapiens*	740
216931	334	13057	CTATGTCCTTGTGTGCACAT	404	*H. sapiens*	741
216932	334	13634	GCCTATTGCCATTTGTATGT	405	*H. sapiens*	742
216933	334	13673	CTATTCATGTCCTTTGCCTA	406	*H. sapiens*	743
216935	334	14567	GATTCTGCGGGTAATCTCAG	408	*H. sapiens*	744
216937	334	14680	TCAATGCAGGTCATTGGAAA	410	*H. sapiens*	745
216938	334	15444	CTACCAGATTGACCATCCCT	411	*H. sapiens*	746
216940	334	15757	TACTTGATAGTGCTCTAGGA	413	*H. sapiens*	747
216941	334	15926	TTGACTGCAGGACCAGGAGG	414	*H. sapiens*	748
216942	334	16245	AACAAACACTTGTGCAAATG	415	*H. sapiens*	749
216950	334	18519	AATGAGACCAAACTTCCACT	423	*H. sapiens*	750
216951	334	18532	TTCCACTTTGAAGCTAGCAA	424	*H. sapiens*	751
216952	334	18586	GATCTGGAGCTTATTCTTGA	425	*H. sapiens*	752
216953	334	18697	ACCTCATGTGACTTGTATGC	426	*H. sapiens*	753
216954	334	18969	TTCTTAAGAAACACCTTGTA	427	*H. sapiens*	754
216955	334	19250	TAGGCCCATCCTGGCTGCAT	428	*H. sapiens*	755
216956	334	19340	AAACTCTCAGGATATGGTAA	429	*H. sapiens*	756
216957	334	19802	ATACCTTCCTCTACCTTTGC	430	*H. sapiens*	757
216958	334	19813	TACCTTTGCTGAAGGTCCTT	431	*H. sapiens*	758
216961	334	20567	ATCTATCTAGTGAAATTTCT	434	*H. sapiens*	759
216962	334	20647	TCAGCTCATCAAAATATGCT	435	*H. sapiens*	760
216963	334	20660	ATATGCTAGTCCTTCCTTTC	436	*H. sapiens*	761
216965	334	21316	CAAAGGTCTGAGTTATCCAG	438	*H. sapiens*	762
216967	334	21422	TGACTTATAGATGCAGGCTG	440	*H. sapiens*	763
216968	334	21634	TCAGTGGAGGGTAATTCTTT	441	*H. sapiens*	764
216969	334	21664	TGCCTAGCCAGTTTGAAAGA	442	*H. sapiens*	765
216970	334	21700	CCTGCAGAATTTTGCCAGGC	443	*H. sapiens*	766
216972	334	22048	GTAGCTAGGTAGGTAAAGCA	445	*H. sapiens*	767
216973	334	22551	TTGAGTGAGACACACAAGGT	446	*H. sapiens*	768
216974	334	22694	GTGCTAGTCAGGGAATGCAT	447	*H. sapiens*	769
216976	334	22903	GGGGAGAGAGCATGCCCAGC	449	*H. sapiens*	770
216977	334	22912	GCATGCCCAGCTGCGAAAGC	450	*H. sapiens*	771
216978	334	23137	AGCCAGGTATAGAAAGGAGT	451	*H. sapiens*	772
216979	334	23170	AACTTTCTAAGAGGCAGAAT	452	*H. sapiens*	773
216981	334	23882	TCTTAGTCTGGTCATGAGTG	454	*H. sapiens*	774
216983	334	24184	AGTAGGAGATTTCATATGAA	456	*H. sapiens*	775
216985	334	24559	TCTTCACCAGCAACACATTA	458	*H. sapiens*	776
216987	334	24800	ATGGCCACCTAGCATGGCAC	460	*H. sapiens*	777
216989	334	24991	CATGTTTCTGAGCCTCCAGA	462	*H. sapiens*	778
216990	334	25067	TAGGTGGCTCCCTGTCTTCA	463	*H. sapiens*	779
216991	334	25152	TCCAAAGTCTTGGGAATCCT	464	*H. sapiens*	780
216995	334	26749	ACAAAGAAAGGGGGAGTTGG	468	*H. sapiens*	781
216996	334	26841	TCGTGTCTTCCTGGCCCAGA	469	*H. sapiens*	782

216997	334	27210	GCAGTGCCCAGCACACAATA	470	*H. sapiens*	783
216998	334	27815	ACTCGTCCAGGTGCGAAGCA	471	*H. sapiens*	784
216999	334	28026	GCCACCTAAGGTAAAGAAGG	472	*H. sapiens*	785
217000	334	28145	ATCAGAGTGGCAGAGAGAGC	473	*H. sapiens*	786
217002	334	28919	TTTACCATAGTTGTGACACA	475	*H. sapiens*	787
217006	334	29871	CATTTTGTAGGCAATGAGCT	479	*H. sapiens*	788
217007	334	30181	GCATTAGTAAACATGAGAAC	480	*H. sapiens*	789
217009	334	30931	TTCATTTCAGCGATGGCCGG	482	*H. sapiens*	790
217013	334	39562	GAAAATCTAGTGTCATTCAA	486	*H. sapiens*	791
217016	334	39789	TCCTATACAGTTTTGGGAAC	489	*H. sapiens*	792
217017	334	39904	AAGGACTTCAGTATGGAGCT	490	*H. sapiens*	793
217018	334	39916	ATGGAGCTTTTATTGAATTG	491	*H. sapiens*	794
217022	334	40412	CCATCAGCACTATTATTTAT	495	*H. sapiens*	795
217023	334	40483	ATAGGCAAGCTCAGCCATAG	496	*H. sapiens*	796
217025	334	40576	TGCTAGATGAGATACATCAA	498	*H. sapiens*	797
217026	334	40658	GAAGACCAAACATGGTTCTA	499	*H. sapiens*	798
217029	334	41130	CTCTGTTTAGTCCTCTCCAG	502	*H. sapiens*	799
217032	503	490	CATTGATAAAATGTTCTGGC	505	*H. sapiens*	800
217033	503	504	TCTGGCACAGCAAAACCTCT	506	*H. sapiens*	801
217034	503	506	TGGCACAGCAAAACCTCTAG	507	*H. sapiens*	802
217037	503	523	TAGAACACATAGTGTGATTT	510	*H. sapiens*	803
217039	503	526	AACACATAGTGTGATTTAAG	512	*H. sapiens*	804

As these "preferred target segments" have been found by experimentation to be open to, and accessible for, hybridization with the antisense compounds of the present invention, one of skill in the art will recognize or be able to ascertain, using no more than routine experimentation, further embodiments of the invention that encompass other compounds that specifically hybridize to these preferred target segments and consequently inhibit the expression of apolipoprotein B.

According to the present invention, antisense compounds include antisense oligomeric compounds, antisense oligonucleotides, ribozymes, external guide sequence (EGS) oligonucleotides, alternate splicers, primers, probes, and other short oligomeric compounds which hybridize to at least a portion of the target nucleic acid.

Example 37

Antisense inhibition of human apolipoprotein B expression - dose response of selected oligonucleotides

In accordance with the present invention, 12 oligonucleotides described in Examples 29 and 31 were further investigated in a dose response study. The control oligonucleotides used in this study were ISIS 18076 (SEQ ID NO: 805) and ISIS 13650 (SEQ ID NO: 806).

All compounds in this study, including the controls, were chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotides. All cytidine residues are 5-methylcytidines.

In the dose-response experiment, with mRNA levels as the endpoint, HepG2 cells were treated with the antisense oligonucleotides or the control oligonucleotides at doses of 37, 75, 150, and 300 nM oligonucleotide. Data were obtained by real-time quantitative PCR as described in other examples herein and are averaged from two experiments with mRNA levels in the treatment groups being normalized to an untreated control group. The data are shown in Table 19.

Table 19

Inhibition of apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Dose Response

Dose

	37 nM	75 nM	150 nM	300 nM	
ISIS #	% inhibition				SEQ ID NO
271009	82	91	94	96	319
281625	62	76	84	94	224
301014	75	90	96	98	249
301027	80	90	95	96	262
301028	70	79	85	92	263
301029	54	67	79	85	264
301030	64	75	87	92	265
301031	61	82	92	96	266
301034	73	87	93	97	269
301036	67	83	92	95	271
301037	73	85	89	96	272
301045	77	86	94	98	280

Example 38

Antisense inhibition of human apolipoprotein B expression - dose response - Lower dose range

In accordance with the present invention, seven oligonucleotides described in Examples 29, 31, 35, and 36 were further investigated in a dose response study. The control oligonucleotides used in this study were ISIS 18076 (SEQ ID NO: 805), ISIS 13650 (SEQ ID NO: 806), and ISIS 129695 (SEQ ID NO: 807).

All compounds in this study, including the controls, were chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotides. All cytidine residues are 5-methylcytidines.

In the dose-response experiment, with mRNA levels as the endpoint, HepG2 cells were treated with the antisense oligonucleotides or the control oligonucleotides at doses

of 12.5, 37, 75, 150, and 300 nM oligonucleotide. Data were obtained by real-time quantitative PCR as described in other examples herein and are averaged from two experiments with mRNA levels in the treatment groups being normalized to an untreated control group. The data are shown in Table 20.

Table 20

Inhibition of apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap - Dose Response

	Dose					
	12.5 nM	37 nM	75 nM	150 nM	300 nM	
ISIS #	% inhibition					SEQ ID #
271009	67	86	92	94	95	319
281625	44	66	83	85	94	224
301012	63	79	90	92	95	247
308638	42	73	91	96	97	247
308642	59	84	91	97	98	319
308651	57	76	84	90	88	319
308658	29	61	73	78	90	224

Example 39

RNA Synthesis

In general, RNA synthesis chemistry is based on the selective incorporation of various protecting groups at strategic intermediary reactions. Although one of ordinary skill in the art will understand the use of protecting groups in organic synthesis, a useful class of protecting groups includes silyl ethers. In particular bulky silyl ethers are used to protect the 5´-hydroxyl in combination with an acid-labile orthoester protecting group on the 2´-hydroxyl. This set of protecting groups is then used with standard solid-phase synthesis technology. It is important

to lastly remove the acid labile orthoester protecting group after all other synthetic steps. Moreover, the early use of the silyl protecting groups during synthesis ensures facile removal when desired, without undesired deprotection of 2′ hydroxyl.

Following this procedure for the sequential protection of the 5′-hydroxyl in combination with protection of the 2′-hydroxyl by protecting groups that are differentially removed and are differentially chemically labile, RNA oligonucleotides were synthesized.

RNA oligonucleotides are synthesized in a stepwise fashion. Each nucleotide is added sequentially (3′- to 5′-direction) to a solid support-bound oligonucleotide. The first nucleoside at the 3′-end of the chain is covalently attached to a solid support. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are added, coupling the second base onto the 5′-end of the first nucleoside. The support is washed and any unreacted 5′-hydroxyl groups are capped with acetic anhydride to yield 5′-acetyl moieties. The linkage is then oxidized to the more stable and ultimately desired P(V) linkage. At the end of the nucleotide addition cycle, the 5′-silyl group is cleaved with fluoride. The cycle is repeated for each subsequent nucleotide.

Following synthesis, the methyl protecting groups on the phosphates are cleaved in 30 minutes utilizing 1 M disodium-2-carbamoyl-2-cyanoethylene-1,1-dithiolate trihydrate (S_2Na_2) in DMF. The deprotection solution is washed from the solid support-bound oligonucleotide using water. The support is then treated with 40% methylamine in water for 10 minutes at 55 °C. This releases the RNA oligonucleotides into solution, deprotects the exocyclic

amines, and modifies the 2´- groups. The oligonucleotides can be analyzed by anion exchange HPLC at this stage.

The 2´-orthoester groups are the last protecting groups to be removed. The ethylene glycol monoacetate orthoester protecting group developed by Dharmacon Research, Inc. (Lafayette, CO), is one example of a useful orthoester protecting group which, has the following important properties. It is stable to the conditions of nucleoside phosphoramidite synthesis and oligonucleotide synthesis. However, after oligonucleotide synthesis the oligonucleotide is treated with methylamine which not only cleaves the oligonucleotide from the solid support but also removes the acetyl groups from the orthoesters. The resulting 2-ethyl-hydroxyl substituents on the orthoester are less electron withdrawing than the acetylated precursor. As a result, the modified orthoester becomes more labile to acid-catalyzed hydrolysis. Specifically, the rate of cleavage is approximately 10 times faster after the acetyl groups are removed. Therefore, this orthoester possesses sufficient stability in order to be compatible with oligonucleotide synthesis and yet, when subsequently modified, permits deprotection to be carried out under relatively mild aqueous conditions compatible with the final RNA oligonucleotide product.

Additionally, methods of RNA synthesis are well known in the art (Scaringe, S. A. Ph.D. Thesis, University of Colorado, 1996; Scaringe, S. A., et al., *J. Am. Chem. Soc.*, **1998**, *120*, 11820-11821; Matteucci, M. D. and Caruthers, M. H. *J. Am. Chem. Soc.*, **1981**, *103*, 3185-3191; Beaucage, S. L. and Caruthers, M. H. *Tetrahedron Lett.*, **1981**, *22*, 1859-1862; Dahl, B. J., et al., *Acta Chem. Scand,*. **1990**, *44*, 639-641; Reddy, M. P., et al., *Tetrahedrom Lett.*, **1994**, *25*,

4311-4314; Wincott, F. et al., *Nucleic Acids Res.*, 1995, *23*, 2677-2684; Griffin, B. E., et al., *Tetrahedron*, 1967, *23*, 2301-2313; Griffin, B. E., et al., *Tetrahedron*, 1967, *23*, 2315-2331).

RNA antisense compounds (RNA oligonucleotides) of the present invention can be synthesized by the methods herein or purchased from Dharmacon Research, Inc (Lafayette, CO). Once synthesized, complementary RNA antisense compounds can then be annealed by methods known in the art to form double stranded (duplexed) antisense compounds. For example, duplexes can be formed by combining 30 μl of each of the complementary strands of RNA oligonucleotides (50 uM RNA oligonucleotide solution) and 15 μl of 5X annealing buffer (100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, 2 mM magnesium acetate) followed by heating for 1 minute at 90°C, then 1 hour at 37°C. The resulting duplexed antisense compounds can be used in kits, assays, screens, or other methods to investigate the role of a target nucleic acid.

Example 40

Design and screening of duplexed antisense compounds targeting apolipoprotein B

In accordance with the present invention, a series of nucleic acid duplexes comprising the antisense compounds of the present invention and their complements can be designed to target apolipoprotein B. The nucleobase sequence of the antisense strand of the duplex comprises at least a portion of an oligonucleotide in Table 1. The ends of the strands may be modified by the addition of one or more natural or modified nucleobases to form an overhang. The sense strand of the dsRNA is then designed and synthesized as the complement of the antisense strand and may also contain

modifications or additions to either terminus. For example, in one embodiment, both strands of the dsRNA duplex would be complementary over the central nucleobases, each having overhangs at one or both termini.

For example, a duplex comprising an antisense strand having the sequence CGAGAGGCGGACGGGACCG and having a two-nucleobase overhang of deoxythymidine(dT) would have the following structure:

```
cgagaggcggacgggaccgTT     Antisense Strand
||||||||||||||||||||
TTgctctccgcctgccctggc     Complement
```

RNA strands of the duplex can be synthesized by methods disclosed herein or purchased from Dharmacon Research Inc., (Lafayette, CO). Once synthesized, the complementary strands are annealed. The single strands are aliquoted and diluted to a concentration of 50 uM. Once diluted, 30 uL of each strand is combined with 15uL of a 5X solution of annealing buffer. The final concentration of said buffer is 100 mM potassium acetate, 30 mM HEPES-KOH pH 7.4, and 2mM magnesium acetate. The final volume is 75 uL. This solution is incubated for 1 minute at 90°C and then centrifuged for 15 seconds. The tube is allowed to sit for 1 hour at 37°C at which time the dsRNA duplexes are used in experimentation. The final concentration of the dsRNA duplex is 20 uM. This solution can be stored frozen (-20°C) and freeze-thawed up to 5 times.

Once prepared, the duplexed antisense compounds are evaluated for their ability to modulate apolipoprotein B expression.

When cells reached 80% confluency, they are treated with duplexed antisense compounds of the invention. For cells grown in 96-well plates, wells are washed once with

200 µL OPTI-MEM-1 reduced-serum medium (Gibco BRL) and then treated with 130 µL of OPTI-MEM-1 containing 12 µg/mL LIPOFECTIN (Gibco BRL) and the desired duplex antisense compound at a final concentration of 200 nM. After 5 hours of treatment, the medium is replaced with fresh medium. Cells are harvested 16 hours after treatment, at which time RNA is isolated and target reduction measured by RT-PCR.

Example 41

Design of phenotypic assays and *in vivo* studies for the use of apolipoprotein B inhibitors

Phenotypic assays

Once apolipoprotein B inhibitors have been identified by the methods disclosed herein, the compounds are further investigated in one or more phenotypic assays, each having measurable endpoints predictive of efficacy in the treatment of a particular disease state or condition. Phenotypic assays, kits and reagents for their use are well known to those skilled in the art and are herein used to investigate the role and/or association of apolipoprotein B in health and disease. Representative phenotypic assays, which can be purchased from any one of several commercial vendors, include those for determining cell viability, cytotoxicity, proliferation or cell survival (Molecular Probes, Eugene, OR; PerkinElmer, Boston, MA), protein-based assays including enzymatic assays (Panvera, LLC, Madison, WI; BD Biosciences, Franklin Lakes, NJ; Oncogene Research Products, San Diego, CA), cell regulation, signal transduction, inflammation, oxidative processes and apoptosis (Assay Designs Inc., Ann Arbor, MI), triglyceride accumulation (Sigma-Aldrich, St. Louis, MO), angiogenesis assays, tube formation assays, cytokine and hormone assays

and metabolic assays (Chemicon International Inc., Temecula, CA; Amersham Biosciences, Piscataway, NJ).

In one non-limiting example, cells determined to be appropriate for a particular phenotypic assay (i.e., MCF-7 cells selected for breast cancer studies; adipocytes for obesity studies) are treated with apolipoprotein B inhibitors identified from the *in vitro* studies as well as control compounds at optimal concentrations which are determined by the methods described above. At the end of the treatment period, treated and untreated cells are analyzed by one or more methods specific for the assay to determine phenotypic outcomes and endpoints.

Phenotypic endpoints include changes in cell morphology over time or treatment dose as well as changes in levels of cellular components such as proteins, lipids, nucleic acids, hormones, saccharides or metals. Measurements of cellular status which include pH, stage of the cell cycle, intake or excretion of biological indicators by the cell, are also endpoints of interest.

Analysis of the geneotype of the cell (measurement of the expression of one or more of the genes of the cell) after treatment is also used as an indicator of the efficacy or potency of the apolipoprotein B inhibitors. Hallmark genes, or those genes suspected to be associated with a specific disease state, condition, or phenotype, are measured in both treated and untreated cells.

In vivo studies

The individual subjects of the *in vivo* studies described herein are warm-blooded vertebrate animals, which includes humans.

The clinical trial is subjected to rigorous controls to ensure that individuals are not unnecessarily put at risk and that they are fully informed about their role in the study.

To account for the psychological effects of receiving treatments, volunteers are randomly given placebo or apolipoprotein B inhibitor. Furthermore, to prevent the doctors from being biased in treatments, they are not informed as to whether the medication they are administering is a apolipoprotein B inhibitor or a placebo. Using this randomization approach, each volunteer has the same chance of being given either the new treatment or the placebo.

Volunteers receive either the apolipoprotein B inhibitor or placebo for eight week period with biological parameters associated with the indicated disease state or condition being measured at the beginning (baseline measurements before any treatment), end (after the final treatment), and at regular intervals during the study period. Such measurements include the levels of nucleic acid molecules encoding apolipoprotein B or apolipoprotein B protein levels in body fluids, tissues or organs compared to pre-treatment levels. Other measurements include, but are not limited to, indices of the disease state or condition being treated, body weight, blood pressure, serum titers of pharmacologic indicators of disease or toxicity as well as ADME (absorption, distribution, metabolism and excretion) measurements.

Information recorded for each patient includes age (years), gender, height (cm), family history of disease state or condition (yes/no), motivation rating

(some/moderate/great) and number and type of previous treatment regimens for the indicated disease or condition.

Volunteers taking part in this study are healthy adults (age 18 to 65 years) and roughly an equal number of males and females participate in the study. Volunteers with certain characteristics are equally distributed for placebo and apolipoprotein B inhibitor treatment. In general, the volunteers treated with placebo have little or no response to treatment, whereas the volunteers treated with the apolipoprotein B inhibitor show positive trends in their disease state or condition index at the conclusion of the study.

Example 42

Antisense inhibition of rabbit apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

In accordance with the present invention, a series of oligonucleotides were designed to target different regions of rabbit apolipoprotein B, using published sequences (GenBank accession number X07480.1, incorporated herein as SEQ ID NO: 808, GenBank accession number M17780.1, incorporated herein as SEQ ID NO: 809, and a sequence was derived using previously described primers (Tanaka, *Journ. Biol. Chem.*, **1993**,*268*, 12713-12718) representing an mRNA of the rabbit apolipoprotein B, incorporated herein as SEQ ID NO: 810). The oligonucleotides are shown in Table 21. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 21 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of

ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl (2'-MOE)nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human apolipoprotein B mRNA levels in primary rabbit hepatocytes by quantitative real-time PCR as described in other examples herein. For rabbit apolipoprotein B the PCR primers were:
forward primer: AAGCACCCCCAATGTCACC (SEQ ID NO: 811)
reverse primer: GGGATGGCAGAGCCAATGTA (SEQ ID NO: 812) and the PCR probe was: FAM- TCCTGGATTCAAGCTTCTATGTGCCTTCA - TAMRA (SEQ ID NO: 813) where FAM (PE-Applied Biosystems, Foster City, CA) is the fluorescent reporter dye) and TAMRA (PE-Applied Biosystems, Foster City, CA) is the quencher dye. Data are averages from two experiments. If present, "N.D." indicates "no data".

Table 21

Inhibition of rabbit apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

ISIS #	TARGET SEQ ID NO	TARGET SITE	SEQUENCE	%INHIB	SEQ ID NO
233149	808	1	TGCTTGGAGAAGGTAAGATC	0	814
233150	810	1	GCGTTGTCTCCGATGTTCTG	20	815
233151	809	13	TAATCATTAACTTGCTGTGG	20	816
233152	808	22	TCAGCACGTAGCAATGCATT	0	817
233153	808	31	GCCTGATACTCAGCACGTAG	0	818
233154	809	31	CAATTGAATGTACTCAGATA	18	819
233155	808	51	ACCTCAGTGACTTGTAATCA	47	820
233156	809	51	CACTGGAAACTTGTCTCTCC	23	821
233157	809	71	AGTAGTTAGTTTCTCCTTGG	0	822
233159	808	121	TCAGTGCCCAAGATGTCAGC	0	823
233160	810	121	ATTGGAATAATGTATCCAGG	81	824
233161	809	130	TTGGCATTATCCAATGCAGT	28	825

233162	808	151	GTTGCCTTGTGAGCAGCAGT	0	826
233163	810	151	ATTGTGAGTGGAGATACTTC	80	827
233164	809	171	CATATGTCTGAAGTTGAGAC	8	828
233165	808	181	GTAGATACTCCATTTTGGCC	0	829
233166	810	181	GGATCACATGACTGAATGCT	82	830
233167	808	201	TCAAGCTGGTTGTTGCACTG	28	831
233168	808	211	GGACTGTACCTCAAGCTGGT	0	832
233169	808	231	GCTCATTCTCCAGCATCAGG	14	833
233170	809	251	TTGATCTATAATACTAGCTA	23	834
233172	810	282	ATGGAAGACTGGCAGCTCTA	86	835
233173	808	301	TTGTGTTCCTTGAAGCGGCC	3	836
233174	809	301	TGTGCACGGATATGATAACG	21	837
233175	810	306	GACCTTGAGTAGATTCCTGG	90	838
233176	810	321	GAAATCTGGAAGAGAGACCT	62	839
233177	808	331	GTAGCTTTCCCATCTAGGCT	0	840
233178	808	346	GATAACTCTGTGAGGGTAGC	0	841
233179	810	371	ATGTTGCCCATGGCTGGAAT	65	842
233180	809	381	AAGATGCAGTACTACTTCCA	13	843
233181	808	382	GCACCCAGAATCATGGCCTG	0	844
233182	809	411	CTTGATACTTGGTATCCACA	59	845
233183	810	411	CAGTGTAATGATCGTTGATT	88	846
233184	810	431	TAAAGTCCAGCATTGGTATT	69	847
233185	810	451	CAACAATGTCTGATTGGTTA	73	848
233186	810	473	GAAGAGGAAGAAAGGATATG	60	849
233187	810	481	TGACAGATGAAGAGGAAGAA	66	850
233188	810	500	TTGTACTGTAGTGCATCAAT	74	851
233189	809	511	GCCTCAATCTGTTGTTTCAG	46	852
233190	810	520	ACTTGAGCGTGCCCTCTAAT	69	853
233191	809	561	GAAATGGAATTGTAGTTCTC	31	854

Example 43

Antisense inhibition of rabbit apolipoprotein B expression by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap-Dose Response Study

In accordance with the present invention, a subset of the antisense oligonuclotides in Example 42 was further investigated in dose-response studies. Treatment doses were 10, 50, 150 and 300 nM. ISIS 233160 (SEQ ID NO: 824), ISIS 233166 (SEQ ID NO: 830), ISIS 233172 (SEQ ID NO: 835), ISIS 233175 (SEQ ID NO: 838), and ISIS 233183 (SEQ ID NO: 846) were analyzed for their effect on rabbit apolipoprotein B mRNA levels in primary rabbit hepatocytes

by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments and are shown in Table 22.

Table 22

Inhibition of rabbit apolipoprotein B mRNA levels by chimeric phosphorothioate oligonucleotides having 2'-MOE wings and a deoxy gap

	Percent Inhibition			
ISIS #	300 nM	150 nM	50 nM	10 nM
233160	80	74	67	33
233166	73	79	81	66
233172	84	81	76	60
233175	93	90	85	67
233183	80	81	71	30

Example 44

Effects of antisense inhibition of apolipoprotein B in LDLr-/- mice - Dose Response

LDL receptor-deficient mice (LDLr(-/-)mice), a strain that cannot edit the apolipoprotein B mRNA and therefore synthesize exclusively apolipoprotein B-100, have markedly elevated LDL cholesterol and apolipoprotein B-100 levels and develop extensive atherosclerosis.

LDLr(-/-) mice, purchased from Taconic (Germantown, NY) were used to evaluate antisense oligonucleotides for their potential to lower apolipoprotein B mRNA or protein levels, as well as phenotypic endpoints associated with apolipoprotein B. LDLr(-/-) mice were separated into groups of males and females. LDLr(-/-) mice were dosed intraperitoneally twice a week for six weeks with either 10, 25, or 50 mg/kg of ISIS 147764 (SEQ ID NO: 109) or ISIS 270906 (SEQ ID NO: 856) which is a 4 base mismatch of ISIS 147764, or with saline, or 20 mg/kg of Atorvastatin. At

study termination animals were sacrificed and evaluated for several phenotypic markers.

ISIS 147764 was able to lower cholesterol, triglycerides, and mRNA levels in a dose-dependent manner in both male and female mice while the 4-base mismatch ISIS 270906 was not able to do this. The results of the study are summarized in Table 23.

Table 23

Effects of ISIS 147764 treatment in male and female LDLr-/- mice on apolipoprotein B mRNA, liver enzyme, cholesterol, and triglyceride levels.

ISIS No.	Dose mg/kg	Liver Enzymes IU/L AST	ALT	Lipoproteins mg/dL CHOL	HDL	LDL	TRIG	mRNA % control
Males								
Saline		68.4	26.6	279.2	125.4	134.7	170.6	100.0
147764	10	57.6	29.8	314.2	150.0	134.7	198.6	61.7
	25	112.6	78.8	185.0	110.6	66.2	104.2	30.7
	50	163.6	156.8	165.6	107.8	51.2	113.4	16.6
270906	50	167.4	348.0	941.0	244.2	541.9	844.8	N.D.
Atorvastatin	20	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	110.9
Females								
Saline		65.0	23.4	265.8	105.8	154.9	121.4	100.0
147764	10	82.0	27.2	269.6	121.0	127.8	140.8	64.2
	25	61.4	32.2	175.8	99.5	68.9	100.4	41.3
	50	134.6	120.4	138.2	92.2	45.9	98.0	18.5
270906	50	96.0	88.6	564.6	200.0	310.0	240.4	N.D.
Atorvastatin	20	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	109.0

Example 45

Effects of antisense inhibition of apolipoprotein B in Cynomolgus monkeys

Cynomolgus monkeys fed an atherogenic diet develop atherosclerosis with many similarities to atherosclerosis of human beings. Female Cynomolgus macaques share several similarities in lipoproteins and the cardiovascular system with humans. In addition to these characteristics, there

are similarities in reproductive biology. The Cynomolgus female has a 28-day menstrual cycle like that of women. Plasma hormone concentrations have been measured throughout the Cynomolgus menstrual cycle, and the duration of the follicular and luteal phases, as well as plasma estradiol and progesterone concentrations across the cycle, are also remarkably similar to those in women.

Cynomolgus monkeys (male or female) can be used to evaluate antisense oligonucleotides for their potential to lower apolipoprotein B mRNA or protein levels, as well as phenotypic endpoints associated with apolipoprotein B including, but not limited to cardiovascular indicators, atherosclerosis, lipid diseases, obesity, and plaque formation. One study could include normal and induced hypercholesterolemic monkeys fed diets that are normal or high in lipid and cholesterol. Cynomolgus monkeys can be dosed in a variety of regimens, one being subcutaneously with 10-20 mg/kg of the oligomeric compound for 1-2 months. Parameters that may observed during the test period could includ: total plasma cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, arterial wall cholesterol content, and coronary intimal thickening.

Example 46

Sequencing of Cynomolgus monkey (Macaca fascicularis) apolipoprotein B preferred target segment

In accordance with the present invention, a portion of the cynomolgus monkey apolipoprotein B mRNA not available in the art, was amplified. Positions 2920 to 3420 of the human apolipoprotein B mRNA sequence (GenBank accession number NM_000384.1, incorporated herein as SEQ ID NO: 3) contain the preferred target segment to which ISIS 301012

hybridizes and the corresponding segment of cynomolgus monkey apolipoprotein B mRNA was amplified and sequenced. The site to which ISIS 301012 hybridizes in the human apolipoprotein B was amplified by placing primers at 5' position 2920 and 3' position 3420. The cynomolgus monkey hepatocytes were purchased from In Vitro Technologies (Gaithersburg, MD). The 500 bp fragments were produced using human and cynomolgus monkey 1° hepatocyte cDNA and were produced by reverse transcription of purified total RNA followed by 40 rounds of PCR amplification. Following gel purification of the human and cynomolgus amplicons, the forward and reverse sequencing reactions of each product were performed by Retrogen (Invitrogen kit was used to create the single-stranded cDNA and provided reagents for Amplitaq PCR reaction). This cynomolgus moneky sequence is incorporated herein as SEQ ID NO: 855 and is 96% identical to positions 2920 to 3420 of the human apolipoprotein B mRNA.

Example 47

Effects of antisense inhibition of human apolipoprotein B gene (ISIS 281625 and 301012) in C57BL/6NTac-TgN(APOB100) transgenic mice

C57BL/6NTac-TgN(APOB100) transgenic mice have the human apolipoprotein B gene "knocked-in". These mice express high levels of human apolipoprotein B100 resulting in mice with elevated serum levels of LDL cholesterol. These mice are useful in identifying and evaluating compounds to reduce elevated levels of LDL cholesterol and the risk of atherosclerosis. When fed a high fat cholesterol diet, these mice develop significant foam cell accumulation underlying the endothelium and within the

media, and have significantly more complex atherosclerotic lesions than control animals.

C57BL/6NTac-TgN(APOB100) mice were divided into two groups - one group receiving oligonucleotide treatment and control animals receiving saline treatment. After overnight fasting, mice were dosed intraperitoneally twice a week with saline or 25 mg/kg ISIS 281625 (SEQ ID No: 224) or ISIS 301012 (SEQ ID No: 247) for eight weeks. At study termination and forty eight hours after the final injections, animals were sacrificed and evaluated for target mRNA levels in liver, cholesterol and triglyceride levels, and liver enzyme levels. In addition, the endogenous mouse apolipoprotein B levels in liver were measured to evaluate any effects of these antisense oligonucletides targeted to the human apolipoprotein B.

Upon treatment with either ISIS 281625 or ISIS 301012, the AST and ALT levels were increased, yet did not exceed normal levels (~300 IU/L). Cholesterol levels were slightly increased relative to saline treatment, while triglyceride levels were slightly decreased. Treatment with either of these oligonucleotides targeted to the human apolipoprotein B which is expressed in these mice markedly decreased the mRNA levels of the human apolipoprotein, while the levels of the endogenous mouse apolipoprotein B were unaffected, indicating that these oligonucleotides exhibit specificity for the human apolipoprotein B. The results of the comparative studies are shown in Table 24.

Table 24

Effects of ISIS 281625 and 301012 treatment in mice on apolipoprotein B mRNA, liver enzyme, cholesterol, and triglyceride levels.

		ISIS No.	
	SALINE	281625	301012
Liver Enzymes IU/L			
AST	70.3	265.8	208.4
ALT	32.8	363.8	137.4
Lipoproteins mg/dL			
CHOL	109.5	152.0	145.1
HDL	67.3	84.6	98.6
LDL	30.2	49.8	36.6
TRIG	194.5	171.1	157.8
mRNA % control			
human mRNA	100.0	45.2	23.7
mouse mRNA	100.0	111.0	94.6

Example 48

Effects of antisense inhibition of apolipoprotein B (ISIS 233172, 233175, 281625, 301012, and 301027) in C57BL/6 mice

C57BL/6 mice, a strain reported to be susceptible to hyperlipidemia-induced atherosclerotic plaque formation were used in the following studies to evaluate the toxicity in mice of several antisense oligonucleotides targeted to human or rabbit apolipoprotein B.

C57BL/6 mice were divided into two groups - one group receiving oligonucleotide treatment and control animals receiving saline treatment. After overnight fasting, mice were dosed intraperitoneally twice a week with saline or 25 mg/kg of one of several oligonucleotides for two weeks. The antisense oligonucleotides used in the present study were ISIS 233172 (SEQ ID NO: 835) and ISIS 233175 (SEQ ID NO: 838), both targeted to rabbit apolipoprotein B, and ISIS 281625 (SEQ ID NO: 224), ISIS 301012 (SEQ ID NO: 247), and ISIS 301027 (SEQ ID NO: 262), targeted to human apolipoprotein B. At study termination and forty eight hours after the final injections, animals were sacrificed and evaluated for liver enzyme levels, body weight, liver weight, and spleen weight.

The levels of liver enzymes in mice were decreased relative to saline treatment for three of the antisense oligonucleotide. However, the rabbit oligonucleotide ISIS 233175 and the human oligonucleotide ISIS 301027 both elicited drastically increased levels of these liver enzymes, indicating toxicity. For all of the oligonucleotides tested, the change in weight of body, liver, and spleen were minor. The results of the comparative studies are shown in Table 25.

Table 25

Effects of antisense oligonucleotides targeted to human or rabbit apolipoprotein B on mouse apolipoprotein B mRNA, liver enzyme, cholesterol, and triglyceride levels.

		ISIS No.				
	SALINE	233172	233175	281625	301012	301027
Liver Enzymes						
AST IU/L	104.5	94.3	346.7	89.5	50.6	455.3
ALT IU/L	39.5	43.3	230.2	36.2	21.2	221.3
Weight						
BODY	21.2	21.3	21.5	20.9	21.3	21.2
LIVER	1.1	1.3	1.4	1.2	1.1	1.3
SPLEEN	0.1	0.1	0.1	0.1	0.1	0.1

Example 49

Time course evaluation of oligonucleotide at two different doses

C57BL/6 mice, a strain reported to be susceptible to hyperlipidemia-induced atherosclerotic plaque formation were used in the following studies to evaluate the toxicity in mice of several antisense oligonucleotides targeted to human apolipoprotein B.

Female C57BL/6 mice were divided into two groups - one group receiving oligonucleotide treatment and control

animals receiving saline treatment. After overnight fasting, mice were dosed intraperitoneally twice a week with saline or 25 mg/kg or 50 mg/kg of ISIS 281625 (SEQ ID NO: 224), ISIS 301012 (SEQ ID NO: 247), or ISIS 301027 (SEQ ID NO: 262). After 2 weeks, a blood sample was taken from the tail of the mice and evaluated for liver enzyme. After 4 weeks, and study termination, animals were sacrificed and evaluated for liver enzyme levels.

For ISIS 281625 and ISIS 301012, AST and ALT levels remained close to those of saline at either dose after 2 weeks. After 4 weeks, AST and ALT levels showed a moderate increase over saline treated animals for the lower dose, but a large increase at the higher dose. ISIS 301027, administered at either dose, showed a small increase in AST and ALT levels after 2 weeks and a huge increase in AST and ALT levels after 4 weeks. The results of the studies are summarized in Table 26.

Table 26

AST and ALT levels in mice treated with ISIS 281625, 301012, or 301027 after 2 and 4 weeks

		AST (IU/L)		ALT (IU/L)	
		2 weeks	4 weeks	2 weeks	4 weeks
SALINE		49.6	63.2	22.4	25.2
ISIS No.	Dose (mg/kg)				
281625	25	40.8	75	21.2	31.8
	50	44.4	152.4	30.8	210.4
301012	25	37.2	89.8	22.4	24.8
	50	38.4	107.4	23.2	29.2
301027	25	55.4	537.6	27.2	311.2
	50	64	1884	34.8	1194

Example 50

Effects of antisense inhibition of apolipoprotein B (ISIS

147483 and 147764) in ob/ob mice

Ob/ob mice receiving a high fat, high cholesterol diet (60% kcal fat supplemented with 0.15% cholesterol) were treated with one of several oligonucleotides to evaluate their effect on apolipoprotein B-related phenotypic endpoints in ob/ob mice. After overnight fasting, mice from each group were dosed intraperitoneally twice a week with 50 mg/kg of ISIS 147483 (SEQ ID NO: 79), or 147764 (SEQ ID NO: 109), or the controls ISIS 116847 (SEQ ID NO: 857), or 141923 (SEQ ID NO:858), or saline for six weeks. At study termination and forty eight hours after the final injections, animals were sacrificed and evaluated for target mRNA levels in liver, cholesterol and triglyceride levels, liver enzyme levels, serum glucose levels, and PTEN levels.

ISIS 147483 and 147764 were both able to lower apolipoprotein B mRNA levels, as well as glucose, cholesterol, and triglyceride levels. The results of the comparative studies are shown in Table 27.

Table 27

Effects of ISIS 147483 and 147764 treatment in ob/ob mice on apolipoprotein B mRNA, cholesterol, lipid, triglyceride, liver enzyme, glucose, and PTEN levels.

		ISIS No.				
		SALINE	116847	141923	147483	147764
Glucose mg/dL		269.6	135.5	328.5	213.2	209.2
Liver Enzymes IU/L	AST	422.3	343.2	329.3	790.2	406.5
	ALT	884.3	607.5	701.7	941.7	835.0
Lipoproteins mg/dL	CHOL	431.9	287.5	646.3	250.0	286.3
	TRIG	128.6	196.5	196.5	99.8	101.2
mRNA % control	ApoB	100.0	77.0	100.0	25.2	43.1
	PTEN	100.0	20.0	113.6	143.2	115.3

What is claimed is:

1. A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound specifically hybridizes with and inhibits the expression of a nucleic acid molecule encoding apolipoprotein B, said compound comprising at least 8 contiguous nucleobases of any one of SEQ ID NOs: 127-134, 136, 138-174, 176-317, 319-321, 323-333, 335-339, 341-374, 376-416, 418-500, 502-510, 512-804, 815, 816, 819-821, 824, 825, 827, 828, 830, 831, 833-835, 837-839, 842, 843, and 845-854.

2. A compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding apolipoprotein B, said compound comprising at least 8 contiguous nucleobases of any one of SEQ ID NOs: 127-134, 136, 138-174, 176-317, 319-321, 323-333, 335-339, 341-374, 376-416, 418-500, 502-510, 512-804, 815, 816, 819-821, 824, 825, 827, 828, 830, 831, 833-835, 837-839, 842, 843, and 845-854, said active site being a region in said nucleic acid wherein binding of said compound to said site significantly inhibits apolipoprotein B expression as compared to a control.

3. A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound specifically hybridizes with said nucleic acid and inhibits expression of apolipoprotein B, wherein the apolipoprotein B is encoded by a polynucleotide selected from the group consisting of: (a) SEQ ID NO: 3 and (b) a naturally occurring variant apolipoprotein B-encoding

polynucleotide that hybridizes to the complement of the polynucleotide of (a) under stringent conditions, said compound comprising at least 8 contiguous nucleobases of any one of SEQ ID NOs: 127-134, 136, 138-174, 176-317, 319-321, 323-333, 335-339, 341-374, 376-416, 418-500, 502-510, 512-804, 815, 816, 819-821, 824, 825, 827, 828, 830, 831, 833-835, 837-839, 842, 843, and 845-854.

4. A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound specifically hybridizes with said nucleic acid and inhibits expression of apolipoprotein B, wherein the apolipoprotein B is encoded by a polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 17, said compound comprising at least 8 contiguous nucleobases of any one of SEQ ID NOs: 127-134, 136, 138-174, 176-317, 319-321, 323-333, 335-339, 341-374, 376-416, 418-500, 502-510, 512-804, 815, 816, 819-821, 824, 825, 827, 828, 830, 831, 833-835, 837-839, 842, 843, and 845-854.

5. A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound specifically hybridizes with an active site in said nucleic acid and inhibits expression of apolipoprotein B, said compound comprising at least 8 contiguous nucleobases of any one of SEQ ID NOs: 127-134, 136, 138-174, 176-317, 319-321, 323-333, 335-339, 341-374, 376-416, 418-500, 502-510, 512-804, 815, 816, 819-821, 824, 825, 827, 828, 830, 831, 833-835, 837-839, 842, 843, and 845-854, said active site being a region in said nucleic acid wherein binding of said compound to said site

significantly inhibits apolipoprotein B expression as compared to a control.

6. An oligonucleotide mimetic compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound specifically hybridizes with said nucleic acid and inhibits expression of apolipoprotein B, said compound comprising at least 8 contiguous nucleobases of any one of SEQ ID NOs: 127-134, 136, 138-174, 176-317, 319-321, 323-333, 335-339, 341-374, 376-416, 418-500, 502-510, 512-804, 815, 816, 819-821, 824, 825, 827, 828, 830, 831, 833-835, 837-839, 842, 843, and 845-854.

7. The compound of any one of claims 1-6 targeted to a nucleic acid molecule encoding apolipoprotein B, wherein said compound specifically hybridizes with and inhibits expression of the long form of apolipoprotein B, ApoB-100.

8. The compound of any one of claims 1-7, wherein said compound specifically hybridizes with said nucleic acid and inhibits expression of mRNA encoding apolipoprotein B by at least 5% in 80% confluent HepG2 cells in culture at an optimum concentration.

9. The compound of claim 8 wherein the compound inhibits expression of mRNA encoding apolipoprotein B by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, or at least 50%.

10. The compound of any one of claims 1-9 which is an antisense oligonucleotide.

11. The compound of any one of claims 1-10 wherein the antisense oligonucleotide has a sequence comprising SEQ ID NO: 224.

12. The compound of any one of claims 1-10 wherein the antisense oligonucleotide hybridizes with a region complementary to SEQ ID NO: 224.

13. The compound of any one of claims 1-10 comprising SEQ ID NO: 224.

14. The compound of any one of claims 1-10 consisting essentially of SEQ ID NO: 224.

15. The compound of any one of claims 1-10 consisting of SEQ ID NO: 224.

16. The compound of any one of claims 1-10 wherein the antisense oligonucleotide has a sequence comprising SEQ ID NO: 247.

17. The compound of any one of claims 1-10 wherein the antisense oligonucleotide hybridizes with a region complementary to SEQ ID NO: 247.

18. The compound of any one of claims 1-10 comprising SEQ ID NO: 247.

19. The compound of any one of claims 1-10 consisting essentially of SEQ ID NO: 247.

20. The compound of any one of claims 1-10 consisting of SEQ ID NO: 247.

21. The compound of any one of claims 1-10 wherein the antisense oligonucleotide has a sequence comprising SEQ ID NO: 319.

22. The compound of any one of claims 1-10 wherein the antisense oligonucleotide hybridizes with a region complementary to SEQ ID NO: 319.

23. The compound of any one of claims 1-10 comprising SEQ ID NO: 319.

24. The compound of any one of claims 1-10 consisting essentially of SEQ ID NO: 319.

25. The compound of any one of claims 1-10 consisting of SEQ ID NO: 319.

26. The compound of any one of claims 1-25 wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage.

27. The compound of claim 26 wherein the modified internucleoside linkage is a phosphorothioate linkage.

28. The compound of any one of claims 1-27 wherein the antisense oligonucleotide comprises at least one modified sugar moiety.

29. The compound of claim 28 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety.

30. The compound of any one of claims 1-29 wherein the

antisense oligonucleotide comprises at least one modified nucleobase.

31. The compound of claim 30 wherein the modified nucleobase is a 5-methylcytosine.

32. The compound of any one of claims 1-31 wherein the antisense oligonucleotide is a chimeric oligonucleotide.

33. A composition comprising the compound of any one of claims 1-32 and a pharmaceutically acceptable carrier or diluent.

34. The composition of claim 33 further comprising a colloidal dispersion system.

35. The composition of claim 33 or 34 wherein the compound is an antisense oligonucleotide.

36. A method of inhibiting the expression of apolipoprotein B in cells or tissues comprising contacting said cells or tissues with the compound of any one of claims 1-32 so that expression of apolipoprotein B is inhibited.

37. A method of treating an animal having a disease or condition associated with apolipoprotein B comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claims 1-32 so that expression of apolipoprotein B is inhibited.

38. The method of claim 37 wherein the condition is associated with abnormal lipid metabolism.

39. The method of claim 37 wherein the condition is associated with abnormal cholesterol metabolism.

40. The method of claim 37 wherein the condition is atherosclerosis.

41. The method of claim 37 wherein the condition is an abnormal metabolic condition.

42. The method of claim 41 wherein the abnormal metabolic condition is hyperlipidemia.

43. The method of claim 37 wherein the disease is diabetes.

44. The method of claim 43 wherein the diabetes is Type 2 diabetes.

45. The method of claim 37 wherein the condition is obesity.

46. The method of claim 37 wherein the disease is cardiovascular disease.

47. A method of modulating glucose levels in an animal comprising administering to said animal the compound of claims 1-32.

48. The method of claim 47 wherein the animal is a human.

49. The method of claim 47 wherein the glucose levels are plasma glucose levels.

50. The method of claim 47 wherein the glucose levels are serum glucose levels.

51. The method of claim 47 wherein the animal is a diabetic animal.

52. A method of preventing or delaying the onset of a disease or condition associated with apolipoprotein B in an animal comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claims 1-32.

53. The method of claim 52 wherein the animal is a human.

54. The method of claim 52 wherein the condition is an abnormal metabolic condition.

55. The method of claim 52 wherein the abnormal metabolic condition is hyperlipidemia.

56. The method of claim 52 wherein the disease is diabetes.

57. The method of claim 56 wherein the diabetes is Type 2 diabetes.

58. The method of claim 52 wherein the condition is obesity.

59. The method of claim 52 wherein the condition is atherosclerosis.

60. The method of claim 52 wherein the condition involves abnormal lipid metabolism.

61. The method of claim 52 wherein the condition involves abnormal cholesterol metabolism.

62. A method of preventing or delaying the onset of an increase in glucose levels in an animal comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claims 1-32.

63. The method of claim 62 wherein the animal is a human.

64. The method of claim 62 wherein the glucose levels are serum glucose levels.

65. The method of claim 62 wherein the glucose levels are plasma glucose levels.

66. A method of modulating serum cholesterol levels in an animal comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claims 1-32.

67. The method of claim 66 wherein the animal is a human.

68. A method of modulating lipoprotein levels in an animal comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claims 1-32.

69. The method of claim 69 wherein the animal is a human.

70. The method of claim 68 wherein the lipoprotein is VLDL.

71. The method of claim 68 wherein the lipoprotein is HDL.

72. The method of claim 68 wherein the lipoprotein is LDL.

73. A method of modulating serum triglyceride levels in an animal comprising administering to said animal a therapeutically or prophylactically effective amount of the compound of claims 1-32.

74. The method of claim 73 wherein the animal is a human.

75. The compound of any one of claims 1-32, wherein said compound specifically hybridizes with and inhibits the expression of a nucleic acid molecule encoding an alternatively spliced form of apolipoprotein B.

76. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of a disease or condition associated with apolipoprotein B expression.

77. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of a condition associated with abnormal lipid metabolism.

78. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of a condition associated with abnormal cholesterol metabolism.

79. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of atherosclerosis.

80. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of hyperlipidemia.

81. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of diabetes.

82. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of Type 2 diabetes.

83. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of obesity.

84. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the treatment of cardiovascular disease.

85. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for preventing or delaying the onset of increased glucose levels.

86. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for preventing or delaying the onset of increased serum glucose levels.

87. Use of a compound of any one of claims 1-32 for the

manufacture of a medicament for preventing or delaying the onset of increased plasma glucose levels.

88. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the modulation of serum cholesterol levels.

89. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the modulation of serum lipoprotein levels.

90. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the modulation of serum VLDL levels.

91. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the modulation of serum HDL levels.

92. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the modulation of serum LDL levels.

93. Use of a compound of any one of claims 1-32 for the manufacture of a medicament for the modulation of serum triglyceride levels.

SEQUENCE LISTING

<110> Rosanne M. Crooke
Mark J. Graham

<120> ANTISENSE MODULATION OF APOLIPOPROTEIN B EXPRESSION

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1 5 10

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Gly Val Pro Gly Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys
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     80                  85                  90

agc cag tgc acc ctg aaa gag gtg tat ggc ttc aac cct gag ggc aaa   458
Ser Gln Cys Thr Leu Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys
 95                 100                 105                 110

gcc ttg ctg aag aaa acc aag aac tct gag gag ttt gct gca gcc atg   506
Ala Leu Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe Ala Ala Ala Met
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Ser Arg Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly Lys Gln Val Phe
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ggc atc att tct gcc ctc ctg gtt ccc cca gag aca gaa gaa gcc aag   650
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175                 180                 185                 190

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Thr Val Lys Thr Arg Lys Gly Asn Val Ala Thr Glu Ile Ser Thr Glu
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    320                 325                 330

cta acc atc tct gag caa aat atc cag aga gct aat ctc ttc aat aag   1178
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335                 340                 345                 350

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                355                 360                 365

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Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu Gln Ala Leu
            370                 375                 380

gtt cag tgt gga cag cct cag tgc tcc act cac atc ctc cag tgg ctg   1322
Val Gln Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu Gln Trp Leu
        385                 390                 395

aaa cgt gtg cat gcc aac ccc ctt ctg ata gat gtg gtc acc tac ctg   1370
Lys Arg Val His Ala Asn Pro Leu Leu Ile Asp Val Val Thr Tyr Leu
    400                 405                 410

gtg gcc ctg atc ccc gag ccc tca gca cag cag ctg cga gag atc ttc   1418
Val Ala Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg Glu Ile Phe
415                 420                 425                 430

aac atg gcg agg gat cag cgc agc cga gcc acc ttg tat gcg ctg agc   1466
Asn Met Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr Ala Leu Ser
                435                 440                 445

cac gcg gtc aac aac tat cat aag aca aac cct aca ggg acc cag gag   1514
His Ala Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly Thr Gln Glu
            450                 455                 460

ctg ctg gac att gct aat tac ctg atg gaa cag att caa gat gac tgc   1562
Leu Leu Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln Asp Asp Cys
        465                 470                 475

act ggg gat gaa gat tac acc tat ttg att ctg cgg gtc att gga aat   1610
Thr Gly Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val Ile Gly Asn
    480                 485                 490

atg ggc caa acc atg gag cag tta act cca gaa ctc aag tct tca atc   1658
Met Gly Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys Ser Ser Ile
495                 500                 505                 510

ctc aaa tgt gtc caa agt aca aag cca tca ctg atg atc cag aaa gct   1706
Leu Lys Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile Gln Lys Ala
                515                 520                 525

gcc atc cag gct ctg cgg aaa atg gag cct aaa gac aag gac cag gag   1754
Ala Ile Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys Asp Gln Glu
            530                 535                 540

gtt ctt ctt cag act ttc ctt gat gat gct tct ccg gga gat aag cga   1802
Val Leu Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly Asp Lys Arg
        545                 550                 555
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ctg gct gcc tat ctt atg ttg atg agg agt cct tca cag gca gat att   1850
Leu Ala Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln Ala Asp Ile
    560                 565                 570

aac aaa att gtc caa att cta cca tgg gaa cag aat gag caa gtg aag   1898
Asn Lys Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu Gln Val Lys
575                 580                 585                 590

aac ttt gtg gct tcc cat att gcc aat atc ttg aac tca gaa gaa ttg   1946
Asn Phe Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser Glu Glu Leu
                595                 600                 605

gat atc caa gat ctg aaa aag tta gtg aaa gaa gct ctg aaa gaa tct   1994
Asp Ile Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu Lys Glu Ser
            610                 615                 620

caa ctt cca act gtc atg gac ttc aga aaa ttc tct cgg aac tat caa   2042
Gln Leu Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg Asn Tyr Gln
        625                 630                 635

ctc tac aaa tct gtt tct ctt cca tca ctt gac cca gcc tca gcc aaa   2090
Leu Tyr Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala Ser Ala Lys
    640                 645                 650

ata gaa ggg aat ctt ata ttt gat cca aat aac tac ctt cct aaa gaa   2138
Ile Glu Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu Pro Lys Glu
655                 660                 665                 670

agc atg ctg aaa act acc ctc act gcc ttt gga ttt gct tca gct gac   2186
Ser Met Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala Ser Ala Asp
                675                 680                 685

ctc atc gag att ggc ttg gaa gga aaa ggc ttt gag cca aca ttg gaa   2234
Leu Ile Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro Thr Leu Glu
            690                 695                 700

gct ctt ttt ggg aag caa gga ttt ttc cca gac agt gtc aac aaa gct   2282
Ala Leu Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val Asn Lys Ala
        705                 710                 715

ttg tac tgg gtt aat ggt caa gtt cct gat ggt gtc tct aag gtc tta   2330
Leu Tyr Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser Lys Val Leu
    720                 725                 730

gtg gac cac ttt ggc tat acc aaa gat gat aaa cat gag cag gat atg   2378
Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu Gln Asp Met
735                 740                 745                 750

gta aat gga ata atg ctc agt gtt gag aag ctg att aaa gat ttg aaa   2426
Val Asn Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys Asp Leu Lys
                755                 760                 765

tcc aaa gaa gtc ccg gaa gcc aga gcc tac ctc cgc atc ttg gga gag   2474
Ser Lys Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Glu
            770                 775                 780

gag ctt ggt ttt gcc agt ctc cat gac ctc cag ctc ctg gga aag ctg   2522
Glu Leu Gly Phe Ala Ser Leu His Asp Leu Gln Leu Leu Gly Lys Leu
        785                 790                 795
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ctt ctg atg ggt gcc cgc act ctg cag ggg atc ccc cag atg att gga   2570
Leu Leu Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln Met Ile Gly
    800                 805                 810

gag gtc atc agg aag ggc tca aag aat gac ttt ttt ctt cac tac atc   2618
Glu Val Ile Arg Lys Gly Ser Lys Asn Asp Phe Phe Leu His Tyr Ile
815                 820                 825                 830

ttc atg gag aat gcc ttt gaa ctc ccc act gga gct gga tta cag ttg   2666
Phe Met Glu Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly Leu Gln Leu
                835                 840                 845

caa ata tct tca tct gga gtc att gct ccc gga gcc aag gct gga gta   2714
Gln Ile Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys Ala Gly Val
            850                 855                 860

aaa ctg gaa gta gcc aac atg cag gct gaa ctg gtg gca aaa ccc tcc   2762
Lys Leu Glu Val Ala Asn Met Gln Ala Glu Leu Val Ala Lys Pro Ser
        865                 870                 875

gtg tct gtg gag ttt gtg aca aat atg ggc atc atc att ccg gac ttc   2810
Val Ser Val Glu Phe Val Thr Asn Met Gly Ile Ile Ile Pro Asp Phe
    880                 885                 890

gct agg agt ggg gtc cag atg aac acc aac ttc ttc cac gag tcg ggt   2858
Ala Arg Ser Gly Val Gln Met Asn Thr Asn Phe Phe His Glu Ser Gly
895                 900                 905                 910

ctg gag gct cat gtt gcc cta aaa gct ggg aag ctg aag ttt atc att   2906
Leu Glu Ala His Val Ala Leu Lys Ala Gly Lys Leu Lys Phe Ile Ile
                915                 920                 925

cct tcc cca aag aga cca gtc aag ctg ctc agt gga ggc aac aca tta   2954
Pro Ser Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly Asn Thr Leu
            930                 935                 940

cat ttg gtc tct acc acc aaa acg gag gtg atc cca cct ctc att gag   3002
His Leu Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro Leu Ile Glu
        945                 950                 955

aac agg cag tcc tgg tca gtt tgc aag caa gtc ttt cct ggc ctg aat   3050
Asn Arg Gln Ser Trp Ser Val Cys Lys Gln Val Phe Pro Gly Leu Asn
    960                 965                 970

tac tgc acc tca ggc gct tac tcc aac gcc agc tcc aca gac tcc gcc   3098
Tyr Cys Thr Ser Gly Ala Tyr Ser Asn Ala Ser Ser Thr Asp Ser Ala
975                 980                 985                 990

tcc tac tat ccg ctg acc ggg gac acc aga tta gag ctg gaa ctg agg   3146
Ser Tyr Tyr Pro Leu Thr Gly Asp Thr Arg Leu Glu Leu Glu Leu Arg
                995                1000                1005

cct aca gga gag att gag cag tat tct gtc agc gca acc tat gag ctc   3194
Pro Thr Gly Glu Ile Glu Gln Tyr Ser Val Ser Ala Thr Tyr Glu Leu
            1010                1015                1020

cag aga gag gac aga gcc ttg gtg gat acc ctg aag ttt gta act caa   3242
Gln Arg Glu Asp Arg Ala Leu Val Asp Thr Leu Lys Phe Val Thr Gln
        1025                1030                1035

gca gaa ggt gcg aag cag act gag gct acc atg aca ttc aaa tat aat   3290
Ala Glu Gly Ala Lys Gln Thr Glu Ala Thr Met Thr Phe Lys Tyr Asn
    1040                1045                1050
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cgg cag agt atg acc ttg tcc agt gaa gtc caa att ccg gat ttt gat   3338
Arg Gln Ser Met Thr Leu Ser Ser Glu Val Gln Ile Pro Asp Phe Asp
1055                1060                1065                1070

gtt gac ctc gga aca atc ctc aga gtt aat gat gaa tct act gag ggc   3386
Val Asp Leu Gly Thr Ile Leu Arg Val Asn Asp Glu Ser Thr Glu Gly
                1075                1080                1085

aaa acg tct tac aga ctc acc ctg gac att cag aac aag aaa att act   3434
Lys Thr Ser Tyr Arg Leu Thr Leu Asp Ile Gln Asn Lys Lys Ile Thr
            1090                1095                1100


gag gtc gcc ctc atg ggc cac cta agt tgt gac aca aag gaa gaa aga   3482
Glu Val Ala Leu Met Gly His Leu Ser Cys Asp Thr Lys Glu Glu Arg
        1105                1110                1115

aaa atc aag ggt gtt att tcc ata ccc cgt ttg caa gca gaa gcc aga   3530
Lys Ile Lys Gly Val Ile Ser Ile Pro Arg Leu Gln Ala Glu Ala Arg
    1120                1125                1130

agt gag atc ctc gcc cac tgg tcg cct gcc aaa ctg ctt ctc caa atg   3578
Ser Glu Ile Leu Ala His Trp Ser Pro Ala Lys Leu Leu Leu Gln Met
1135                1140                1145                1150

gac tca tct gct aca gct tat ggc tcc aca gtt tcc aag agg gtg gca   3626
Asp Ser Ser Ala Thr Ala Tyr Gly Ser Thr Val Ser Lys Arg Val Ala
                1155                1160                1165

tgg cat tat gat gaa gag aag att gaa ttt gaa tgg aac aca ggc acc   3674
Trp His Tyr Asp Glu Glu Lys Ile Glu Phe Glu Trp Asn Thr Gly Thr
            1170                1175                1180

aat gta gat acc aaa aaa atg act tcc aat ttc cct gtg gat ctc tcc   3722
Asn Val Asp Thr Lys Lys Met Thr Ser Asn Phe Pro Val Asp Leu Ser
        1185                1190                1195

gat tat cct aag agc ttg cat atg tat gct aat aga ctc ctg gat cac   3770
Asp Tyr Pro Lys Ser Leu His Met Tyr Ala Asn Arg Leu Leu Asp His
    1200                1205                1210

aga gtc cct gaa aca gac atg act ttc cgg cac gtg ggt tcc aaa tta   3818
Arg Val Pro Glu Thr Asp Met Thr Phe Arg His Val Gly Ser Lys Leu
1215                1220                1225                1230

ata gtt gca atg agc tca tgg ctt cag aag gca tct ggg agt ctt cct   3866
Ile Val Ala Met Ser Ser Trp Leu Gln Lys Ala Ser Gly Ser Leu Pro
                1235                1240                1245

tat acc cag act ttg caa gac cac ctc aat agc ctg aag gag ttc aac   3914
Tyr Thr Gln Thr Leu Gln Asp His Leu Asn Ser Leu Lys Glu Phe Asn
            1250                1255                1260

ctc cag aac atg gga ttg cca gac ttc cac atc cca gaa aac ctc ttc   3962
Leu Gln Asn Met Gly Leu Pro Asp Phe His Ile Pro Glu Asn Leu Phe
        1265                1270                1275

tta aaa agc gat ggc cgg gtc aaa tat acc ttg aac aag aac agt ttg   4010
Leu Lys Ser Asp Gly Arg Val Lys Tyr Thr Leu Asn Lys Asn Ser Leu
    1280                1285                1290
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aaa att gag att cct ttg cct ttt ggt ggc aaa tcc tcc aga gat cta   4058
Lys Ile Glu Ile Pro Leu Pro Phe Gly Gly Lys Ser Ser Arg Asp Leu
1295                1300                1305                1310

aag atg tta gag act gtt agg aca cca gcc ctc cac ttc aag tct gtg   4106
Lys Met Leu Glu Thr Val Arg Thr Pro Ala Leu His Phe Lys Ser Val
                1315                1320                1325

gga ttc cat ctg cca tct cga gag ttc caa gtc cct act ttt acc att   4154
Gly Phe His Leu Pro Ser Arg Glu Phe Gln Val Pro Thr Phe Thr Ile
            1330                1335                1340

ccc aag ttg tat caa ctg caa gtg cct ctc ctg ggt gtt cta gac ctc   4202
Pro Lys Leu Tyr Gln Leu Gln Val Pro Leu Leu Gly Val Leu Asp Leu
        1345                1350                1355

tcc acg aat gtc tac agc aac ttg tac aac tgg tcc gcc tcc tac agt   4250
Ser Thr Asn Val Tyr Ser Asn Leu Tyr Asn Trp Ser Ala Ser Tyr Ser
    1360                1365                1370

ggt ggc aac acc agc aca gac cat ttc agc ctt cgg gct cgt tac cac   4298
Gly Gly Asn Thr Ser Thr Asp His Phe Ser Leu Arg Ala Arg Tyr His
1375                1380                1385                1390

atg aag gct gac tct gtg gtt gac ctg ctt tcc tac aat gtg caa gga   4346
Met Lys Ala Asp Ser Val Val Asp Leu Leu Ser Tyr Asn Val Gln Gly
                1395                1400                1405

tct gga gaa aca aca tat gac cac aag aat acg ttc aca cta tca tgt   4394
Ser Gly Glu Thr Thr Tyr Asp His Lys Asn Thr Phe Thr Leu Ser Cys
            1410                1415                1420

gat ggg tct cta cgc cac aaa ttt cta gat tcg aat atc aaa ttc agt   4442
Asp Gly Ser Leu Arg His Lys Phe Leu Asp Ser Asn Ile Lys Phe Ser
        1425                1430                1435

cat gta gaa aaa ctt gga aac aac cca gtc tca aaa ggt tta cta ata   4490
His Val Glu Lys Leu Gly Asn Asn Pro Val Ser Lys Gly Leu Leu Ile
    1440                1445                1450

ttc gat gca tct agt tcc tgg gga cca cag atg tct gct tca gtt cat   4538
Phe Asp Ala Ser Ser Ser Trp Gly Pro Gln Met Ser Ala Ser Val His
1455                1460                1465                1470

ttg gac tcc aaa aag aaa cag cat ttg ttt gtc aaa gaa gtc aag att   4586
Leu Asp Ser Lys Lys Lys Gln His Leu Phe Val Lys Glu Val Lys Ile
                1475                1480                1485

gat ggg cag ttc aga gtc tct tcg ttc tat gct aaa ggc aca tat ggc   4634
Asp Gly Gln Phe Arg Val Ser Ser Phe Tyr Ala Lys Gly Thr Tyr Gly
            1490                1495                1500

ctg tct tgt cag agg gat cct aac act ggc cgg ctc aat gga gag tcc   4682
Leu Ser Cys Gln Arg Asp Pro Asn Thr Gly Arg Leu Asn Gly Glu Ser
        1505                1510                1515

aac ctg agg ttt aac tcc tcc tac ctc caa ggc acc aac cag ata aca   4730
Asn Leu Arg Phe Asn Ser Ser Tyr Leu Gln Gly Thr Asn Gln Ile Thr
    1520                1525                1530

gga aga tat gaa gat gga acc ctc tcc ctc acc tcc acc tct gat ctg   4778
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Gly Arg Tyr Glu Asp Gly Thr Leu Ser Leu Thr Ser Thr Ser Asp Leu
1535                1540                1545                1550

caa agt ggc atc att aaa aat act gct tcc cta aag tat gag aac tac   4826
Gln Ser Gly Ile Ile Lys Asn Thr Ala Ser Leu Lys Tyr Glu Asn Tyr
            1555                1560                1565

gag ctg act tta aaa tct gac acc aat ggg aag tat aag aac ttt gcc   4874
Glu Leu Thr Leu Lys Ser Asp Thr Asn Gly Lys Tyr Lys Asn Phe Ala
        1570                1575                1580

act tct aac aag atg gat atg acc ttc tct aag caa aat gca ctg ctg   4922
Thr Ser Asn Lys Met Asp Met Thr Phe Ser Lys Gln Asn Ala Leu Leu
    1585                1590                1595

cgt tct gaa tat cag gct gat tac gag tca ttg agg ttc ttc agc ctg   4970
Arg Ser Glu Tyr Gln Ala Asp Tyr Glu Ser Leu Arg Phe Phe Ser Leu
1600                1605                1610

ctt tct gga tca cta aat tcc cat ggt ctt gag tta aat gct gac atc   5018
Leu Ser Gly Ser Leu Asn Ser His Gly Leu Glu Leu Asn Ala Asp Ile
1615                1620                1625                1630

tta ggc act gac aaa att aat agt ggt gct cac aag gcg aca cta agg   5066
Leu Gly Thr Asp Lys Ile Asn Ser Gly Ala His Lys Ala Thr Leu Arg
                1635                1640                1645

att ggc caa gat gga ata tct acc agt gca acg acc aac ttg aag tgt   5114
Ile Gly Gln Asp Gly Ile Ser Thr Ser Ala Thr Thr Asn Leu Lys Cys
            1650                1655                1660

agt ctc ctg gtg ctg gag aat gag ctg aat gca gag ctt ggc ctc tct   5162
Ser Leu Leu Val Leu Glu Asn Glu Leu Asn Ala Glu Leu Gly Leu Ser
        1665                1670                1675

ggg gca tct atg aaa tta aca aca aat ggc cgc ttc agg gaa cac aat   5210
Gly Ala Ser Met Lys Leu Thr Thr Asn Gly Arg Phe Arg Glu His Asn
    1680                1685                1690

gca aaa ttc agt ctg gat ggg aaa gcc gcc ctc aca gag cta tca ctg   5258
Ala Lys Phe Ser Leu Asp Gly Lys Ala Ala Leu Thr Glu Leu Ser Leu
1695                1700                1705                1710

gga agt gct tat cag gcc atg att ctg ggt gtc gac agc aaa aac att   5306
Gly Ser Ala Tyr Gln Ala Met Ile Leu Gly Val Asp Ser Lys Asn Ile
                1715                1720                1725

ttc aac ttc aag gtc agt caa gaa gga ctt aag ctc tca aat gac atg   5354
Phe Asn Phe Lys Val Ser Gln Glu Gly Leu Lys Leu Ser Asn Asp Met
            1730                1735                1740

atg ggc tca tat gct gaa atg aaa ttt gac cac aca aac agt ctg aac   5402
Met Gly Ser Tyr Ala Glu Met Lys Phe Asp His Thr Asn Ser Leu Asn
        1745                1750                1755

att gca ggc tta tca ctg gac ttc tct tca aaa ctt gac aac att tac   5450
Ile Ala Gly Leu Ser Leu Asp Phe Ser Ser Lys Leu Asp Asn Ile Tyr
    1760                1765                1770


agc tct gac aag ttt tat aag caa act gtt aat tta cag cta cag ccc   5498
Ser Ser Asp Lys Phe Tyr Lys Gln Thr Val Asn Leu Gln Leu Gln Pro
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1775                1780                1785                1790

tat tct ctg gta act act tta aac agt gac ctg aaa tac aat gct ctg   5546
Tyr Ser Leu Val Thr Thr Leu Asn Ser Asp Leu Lys Tyr Asn Ala Leu
                1795                1800                1805

gat ctc acc aac aat ggg aaa cta cgg cta gaa ccc ctg aag ctg cat   5594
Asp Leu Thr Asn Asn Gly Lys Leu Arg Leu Glu Pro Leu Lys Leu His
            1810                1815                1820

gtg gct ggt aac cta aaa gga gcc tac caa aat aat gaa ata aaa cac   5642
Val Ala Gly Asn Leu Lys Gly Ala Tyr Gln Asn Asn Glu Ile Lys His
        1825                1830                1835

atc tat gcc atc tct tct gct gcc tta tca gca agc tat aaa gca gac   5690
Ile Tyr Ala Ile Ser Ser Ala Ala Leu Ser Ala Ser Tyr Lys Ala Asp
    1840                1845                1850

act gtt gct aag gtt cag ggt gtg gag ttt agc cat cgg ctc aac aca   5738
Thr Val Ala Lys Val Gln Gly Val Glu Phe Ser His Arg Leu Asn Thr
1855                1860                1865                1870

gac atc gct ggg ctg gct tca gcc att gac atg agc aca aac tat aat   5786
Asp Ile Ala Gly Leu Ala Ser Ala Ile Asp Met Ser Thr Asn Tyr Asn
                1875                1880                1885

tca gac tca ctg cat ttc agc aat gtc ttc cgt tct gta atg gcc ccg   5834
Ser Asp Ser Leu His Phe Ser Asn Val Phe Arg Ser Val Met Ala Pro
            1890                1895                1900

ttt acc atg acc atc gat gca cat aca aat ggc aat ggg aaa ctc gct   5882
Phe Thr Met Thr Ile Asp Ala His Thr Asn Gly Asn Gly Lys Leu Ala
        1905                1910                1915

ctc tgg gga gaa cat act ggg cag ctg tat agc aaa ttc ctg ttg aaa   5930
Leu Trp Gly Glu His Thr Gly Gln Leu Tyr Ser Lys Phe Leu Leu Lys
    1920                1925                1930

gca gaa cct ctg gca ttt act ttc tct cat gat tac aaa ggc tcc aca   5978
Ala Glu Pro Leu Ala Phe Thr Phe Ser His Asp Tyr Lys Gly Ser Thr
1935                1940                1945                1950

agt cat cat ctc gtg tct agg aaa agc atc agt gca gct ctt gaa cac   6026
Ser His His Leu Val Ser Arg Lys Ser Ile Ser Ala Ala Leu Glu His
                1955                1960                1965

aaa gtc agt gcc ctg ctt act cca gct gag cag aca ggc acc tgg aaa   6074
Lys Val Ser Ala Leu Leu Thr Pro Ala Glu Gln Thr Gly Thr Trp Lys
            1970                1975                1980

ctc aag acc caa ttt aac aac aat gaa tac agc cag gac ttg gat gct   6122
Leu Lys Thr Gln Phe Asn Asn Asn Glu Tyr Ser Gln Asp Leu Asp Ala
        1985                1990                1995

tac aac act aaa gat aaa att ggc gtg gag ctt act gga cga act ctg   6170
Tyr Asn Thr Lys Asp Lys Ile Gly Val Glu Leu Thr Gly Arg Thr Leu
    2000                2005                2010

gct gac cta act cta cta gac tcc cca att aaa gtg cca ctt tta ctc   6218
Ala Asp Leu Thr Leu Leu Asp Ser Pro Ile Lys Val Pro Leu Leu Leu
2015                2020                2025                2030

agt gag ccc atc aat atc att gat gct tta gag atg aga gat gcc gtt   6266
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Ser Glu Pro Ile Asn Ile Ile Asp Ala Leu Glu Met Arg Asp Ala Val
                2035                2040                2045

gag aag ccc caa gaa ttt aca att gtt gct ttt gta aag tat gat aaa   6314
Glu Lys Pro Gln Glu Phe Thr Ile Val Ala Phe Val Lys Tyr Asp Lys
            2050                2055                2060

aac caa gat gtt cac tcc att aac ctc cca ttt ttt gag acc ttg caa   6362
Asn Gln Asp Val His Ser Ile Asn Leu Pro Phe Phe Glu Thr Leu Gln
        2065                2070                2075

gaa tat ttt gag agg aat cga caa acc att ata gtt gta gtg gaa aac   6410
Glu Tyr Phe Glu Arg Asn Arg Gln Thr Ile Ile Val Val Val Glu Asn
    2080                2085                2090

gta cag aga aac ctg aag cac atc aat att gat caa ttt gta aga aaa   6458
Val Gln Arg Asn Leu Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys
2095                2100                2105                2110

tac aga gca gcc ctg gga aaa ctc cca cag caa gct aat gat tat ctg   6506
Tyr Arg Ala Ala Leu Gly Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu
                2115                2120                2125

aat tca ttc aat tgg gag aga caa gtt tca cat gcc aag gag aaa ctg   6554
Asn Ser Phe Asn Trp Glu Arg Gln Val Ser His Ala Lys Glu Lys Leu
            2130                2135                2140

act gct ctc aca aaa aag tat aga att aca gaa aat gat ata caa att   6602
Thr Ala Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp Ile Gln Ile
        2145                2150                2155

gca tta gat gat gcc aaa atc aac ttt aat gaa aaa cta tct caa ctg   6650
Ala Leu Asp Asp Ala Lys Ile Asn Phe Asn Glu Lys Leu Ser Gln Leu
    2160                2165                2170

cag aca tat atg ata caa ttt gat cag tat att aaa gat agt tat gat   6698
Gln Thr Tyr Met Ile Gln Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp
2175                2180                2185                2190

tta cat gat ttg aaa ata gct att gct aat att att gat gaa atc att   6746
Leu His Asp Leu Lys Ile Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile
                2195                2200                2205

gaa aaa tta aaa agt ctt gat gag cac tat cat atc cgt gta aat tta   6794
Glu Lys Leu Lys Ser Leu Asp Glu His Tyr His Ile Arg Val Asn Leu
            2210                2215                2220

gta aaa aca atc cat gat cta cat ttg ttt att gaa aat att gat ttt   6842
Val Lys Thr Ile His Asp Leu His Leu Phe Ile Glu Asn Ile Asp Phe
        2225                2230                2235

aac aaa agt gga agt agt act gca tcc tgg att caa aat gtg gat act   6890
Asn Lys Ser Gly Ser Ser Thr Ala Ser Trp Ile Gln Asn Val Asp Thr
    2240                2245                2250

aag tac caa atc aga atc cag ata caa gaa aaa ctg cag cag ctt aag   6938
Lys Tyr Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln Leu Lys
2255                2260                2265                2270

aga cac ata cag aat ata gac atc cag cac cta gct gga aag tta aaa   6986
Arg His Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys Leu Lys
                2275                2280                2285
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caa cac att gag gct att gat gtt aga gtg ctt tta gat caa ttg gga   7034
Gln His Ile Glu Ala Ile Asp Val Arg Val Leu Leu Asp Gln Leu Gly
            2290                2295                2300

act aca att tca ttt gaa aga ata aat gat gtt ctt gag cat gtc aaa   7082
Thr Thr Ile Ser Phe Glu Arg Ile Asn Asp Val Leu Glu His Val Lys
        2305                2310                2315

cac ttt gtt ata aat ctt att ggg gat ttt gaa gta gct gag aaa atc   7130
His Phe Val Ile Asn Leu Ile Gly Asp Phe Glu Val Ala Glu Lys Ile
    2320                2325                2330

aat gcc ttc aga gcc aaa gtc cat gag tta atc gag agg tat gaa gta   7178
Asn Ala Phe Arg Ala Lys Val His Glu Leu Ile Glu Arg Tyr Glu Val
2335                2340                2345                2350

gac caa caa atc cag gtt tta atg gat aaa tta gta gag ttg acc cac   7226
Asp Gln Gln Ile Gln Val Leu Met Asp Lys Leu Val Glu Leu Thr His
                2355                2360                2365

caa tac aag ttg aag gag act att cag aag cta agc aat gtc cta caa   7274
Gln Tyr Lys Leu Lys Glu Thr Ile Gln Lys Leu Ser Asn Val Leu Gln
            2370                2375                2380

caa gtt aag ata aaa gat tac ttt gag aaa ttg gtt gga ttt att gat   7322
Gln Val Lys Ile Lys Asp Tyr Phe Glu Lys Leu Val Gly Phe Ile Asp
        2385                2390                2395

gat gct gtg aag aag ctt aat gaa tta tct ttt aaa aca ttc att gaa   7370
Asp Ala Val Lys Lys Leu Asn Glu Leu Ser Phe Lys Thr Phe Ile Glu
    2400                2405                2410

gat gtt aac aaa ttc ctt gac atg ttg ata aag aaa tta aag tca ttt   7418
Asp Val Asn Lys Phe Leu Asp Met Leu Ile Lys Lys Leu Lys Ser Phe
2415                2420                2425                2430

gat tac cac cag ttt gta gat gaa acc aat gac aaa atc cgt gag gtg   7466
Asp Tyr His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile Arg Glu Val
                2435                2440                2445

act cag aga ctc aat ggt gaa att cag gct ctg gaa cta cca caa aaa   7514
Thr Gln Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu Pro Gln Lys
            2450                2455                2460

gct gaa gca tta aaa ctg ttt tta gag gaa acc aag gcc aca gtt gca   7562
Ala Glu Ala Leu Lys Leu Phe Leu Glu Glu Thr Lys Ala Thr Val Ala
        2465                2470                2475

gtg tat ctg gaa agc cta cag gac acc aaa ata acc tta atc atc aat   7610
Val Tyr Leu Glu Ser Leu Gln Asp Thr Lys Ile Thr Leu Ile Ile Asn
    2480                2485                2490

tgg tta cag gag gct tta agt tca gca tct ttg gct cac atg aag gcc   7658
Trp Leu Gln Glu Ala Leu Ser Ser Ala Ser Leu Ala His Met Lys Ala
2495                2500                2505                2510

aaa ttc cga gag act cta gaa gat aca cga gac cga atg tat caa atg   7706
Lys Phe Arg Glu Thr Leu Glu Asp Thr Arg Asp Arg Met Tyr Gln Met
                2515                2520                2525

gac att cag cag gaa ctt caa cga tac ctg tct ctg gta ggc cag gtt   7754
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Asp Ile Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val Gly Gln Val
          2530                2535                2540

tat agc aca ctt gtc acc tac att tct gat tgg tgg act ctt gct gct   7802
Tyr Ser Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr Leu Ala Ala
       2545                2550                2555

aag aac ctt act gac ttt gca gag caa tat tct atc caa gat tgg gct   7850
Lys Asn Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln Asp Trp Ala
    2560                2565                2570

aaa cgt atg aaa gca ttg gta gag caa ggg ttc act gtt cct gaa atc   7898
Lys Arg Met Lys Ala Leu Val Glu Gln Gly Phe Thr Val Pro Glu Ile
2575                2580                2585                2590

aag acc atc ctt ggg acc atg cct gcc ttt gaa gtc agt ctt cag gct   7946
Lys Thr Ile Leu Gly Thr Met Pro Ala Phe Glu Val Ser Leu Gln Ala
                2595                2600                2605

ctt cag aaa gct acc ttc cag aca cct gat ttt ata gtc ccc cta aca   7994
Leu Gln Lys Ala Thr Phe Gln Thr Pro Asp Phe Ile Val Pro Leu Thr
          2610                2615                2620

gat ttg agg att cca tca gtt cag ata aac ttc aaa gac tta aaa aat   8042
Asp Leu Arg Ile Pro Ser Val Gln Ile Asn Phe Lys Asp Leu Lys Asn
       2625                2630                2635

ata aaa atc cca tcc agg ttt tcc aca cca gaa ttt acc atc ctt aac   8090
Ile Lys Ile Pro Ser Arg Phe Ser Thr Pro Glu Phe Thr Ile Leu Asn
    2640                2645                2650

acc ttc cac att cct tcc ttt aca att gac ttt gtc gaa atg aaa gta   8138
Thr Phe His Ile Pro Ser Phe Thr Ile Asp Phe Val Glu Met Lys Val
2655                2660                2665                2670

aag atc atc aga acc att gac cag atg cag aac agt gag ctg cag tgg   8186
Lys Ile Ile Arg Thr Ile Asp Gln Met Gln Asn Ser Glu Leu Gln Trp
                2675                2680                2685

ccc gtt cca gat ata tat ctc agg gat ctg aag gtg gag gac att cct   8234
Pro Val Pro Asp Ile Tyr Leu Arg Asp Leu Lys Val Glu Asp Ile Pro
          2690                2695                2700

cta gcg aga atc acc ctg cca gac ttc cgt tta cca gaa atc gca att   8282
Leu Ala Arg Ile Thr Leu Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile
       2705                2710                2715

cca gaa ttc ata atc cca act ctc aac ctt aat gat ttt caa gtt cct   8330
Pro Glu Phe Ile Ile Pro Thr Leu Asn Leu Asn Asp Phe Gln Val Pro
    2720                2725                2730

gac ctt cac ata cca gaa ttc cag ctt ccc cac atc tca cac aca att   8378
Asp Leu His Ile Pro Glu Phe Gln Leu Pro His Ile Ser His Thr Ile
2735                2740                2745                2750

gaa gta cct act ttt ggc aag cta tac agt att ctg aaa atc caa tct   8426
Glu Val Pro Thr Phe Gly Lys Leu Tyr Ser Ile Leu Lys Ile Gln Ser
                2755                2760                2765

cct ctt ttc aca tta gat gca aat gct gac ata ggg aat gga acc acc   8474
Pro Leu Phe Thr Leu Asp Ala Asn Ala Asp Ile Gly Asn Gly Thr Thr
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          2770                2775                2780

tca gca aac gaa gca ggt atc gca gct tcc atc act gcc aaa gga gag   8522
Ser Ala Asn Glu Ala Gly Ile Ala Ala Ser Ile Thr Ala Lys Gly Glu
        2785                2790                2795

tcc aaa tta gaa gtt ctc aat ttt gat ttt caa gca aat gca caa ctc   8570
Ser Lys Leu Glu Val Leu Asn Phe Asp Phe Gln Ala Asn Ala Gln Leu
    2800                2805                2810

tca aac cct aag att aat ccg ctg gct ctg aag gag tca gtg aag ttc   8618
Ser Asn Pro Lys Ile Asn Pro Leu Ala Leu Lys Glu Ser Val Lys Phe
2815                2820                2825                2830

tcc agc aag tac ctg aga acg gag cat ggg agt gaa atg ctg ttt ttt   8666
Ser Ser Lys Tyr Leu Arg Thr Glu His Gly Ser Glu Met Leu Phe Phe
                2835                2840                2845

gga aat gct att gag gga aaa tca aac aca gtg gca agt tta cac aca   8714
Gly Asn Ala Ile Glu Gly Lys Ser Asn Thr Val Ala Ser Leu His Thr
            2850                2855                2860

gaa aaa aat aca ctg gag ctt agt aat gga gtg att gtc aag ata aac   8762
Glu Lys Asn Thr Leu Glu Leu Ser Asn Gly Val Ile Val Lys Ile Asn
        2865                2870                2875

aat cag ctt acc ctg gat agc aac act aaa tac ttc cac aaa ttg aac   8810
Asn Gln Leu Thr Leu Asp Ser Asn Thr Lys Tyr Phe His Lys Leu Asn
    2880                2885                2890

atc ccc aaa ctg gac ttc tct agt cag gct gac ctg cgc aac gag atc   8858
Ile Pro Lys Leu Asp Phe Ser Ser Gln Ala Asp Leu Arg Asn Glu Ile
2895                2900                2905                2910

aag aca ctg ttg aaa gct ggc cac ata gca tgg act tct tct gga aaa   8906
Lys Thr Leu Leu Lys Ala Gly His Ile Ala Trp Thr Ser Ser Gly Lys
                2915                2920                2925

ggg tca tgg aaa tgg gcc tgc ccc aga ttc tca gat gag gga aca cat   8954
Gly Ser Trp Lys Trp Ala Cys Pro Arg Phe Ser Asp Glu Gly Thr His
            2930                2935                2940

gaa tca caa att agt ttc acc ata gaa gga ccc ctc act tcc ttt gga   9002
Glu Ser Gln Ile Ser Phe Thr Ile Glu Gly Pro Leu Thr Ser Phe Gly
        2945                2950                2955

ctg tcc aat aag atc aat agc aaa cac cta aga gta aac caa aac ttg   9050
Leu Ser Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln Asn Leu
    2960                2965                2970

gtt tat gaa tct ggc tcc ctc aac ttt tct aaa ctt gaa att caa tca   9098
Val Tyr Glu Ser Gly Ser Leu Asn Phe Ser Lys Leu Glu Ile Gln Ser
2975                2980                2985                2990

caa gtc gat tcc cag cat gtg ggc cac agt gtt cta act gct aaa ggc   9146
Gln Val Asp Ser Gln His Val Gly His Ser Val Leu Thr Ala Lys Gly
                2995                3000                3005

atg gca ctg ttt gga gaa ggg aag gca gag ttt act ggg agg cat gat   9194
Met Ala Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly Arg His Asp
            3010                3015                3020

gct cat tta aat gga aag gtt att gga act ttg aaa aat tct ctt ttc   9242
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Ala His Leu Asn Gly Lys Val Ile Gly Thr Leu Lys Asn Ser Leu Phe
        3025                3030                3035

ttt tca gcc cag cca ttt gag atc acg gca tcc aca aac aat gaa ggg   9290
Phe Ser Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn Asn Glu Gly
    3040                3045                3050

aat ttg aaa gtt cgt ttt cca tta agg tta aca ggg aag ata gac ttc   9338
Asn Leu Lys Val Arg Phe Pro Leu Arg Leu Thr Gly Lys Ile Asp Phe
3055                3060                3065                3070

ctg aat aac tat gca ctg ttt ctg agt ccc agt gcc cag caa gca agt   9386
Leu Asn Asn Tyr Ala Leu Phe Leu Ser Pro Ser Ala Gln Gln Ala Ser
                3075                3080                3085

tgg caa gta agt gct agg ttc aat cag tat aag tac aac caa aat ttc   9434
Trp Gln Val Ser Ala Arg Phe Asn Gln Tyr Lys Tyr Asn Gln Asn Phe
            3090                3095                3100

tct gct gga aac aac gag aac att atg gag gcc cat gta gga ata aat   9482
Ser Ala Gly Asn Asn Glu Asn Ile Met Glu Ala His Val Gly Ile Asn
        3105                3110                3115

gga gaa gca aat ctg gat ttc tta aac att cct tta aca att cct gaa   9530
Gly Glu Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr Ile Pro Glu
    3120                3125                3130

atg cgt cta cct tac aca ata atc aca act cct cca ctg aaa gat ttc   9578
Met Arg Leu Pro Tyr Thr Ile Ile Thr Thr Pro Pro Leu Lys Asp Phe
3135                3140                3145                3150

tct cta tgg gaa aaa aca ggc ttg aag gaa ttc ttg aaa acg aca aag   9626
Ser Leu Trp Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys
                3155                3160                3165

caa tca ttt gat tta agt gta aaa gct cag tat aag aaa aac aaa cac   9674
Gln Ser Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys His
            3170                3175                3180

agg cat tcc atc aca aat cct ttg gct gtg ctt tgt gag ttt atc agt   9722
Arg His Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu Phe Ile Ser
        3185                3190                3195

cag agc atc aaa tcc ttt gac agg cat ttt gaa aaa aac aga aac aat   9770
Gln Ser Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn Asn
    3200                3205                3210

gca tta gat ttt gtc acc aaa tcc tat aat gaa aca aaa att aag ttt   9818
Ala Leu Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile Lys Phe
3215                3220                3225                3230

gat aag tac aaa gct gaa aaa tct cac gac gag ctc ccc agg acc ttt   9866
Asp Lys Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro Arg Thr Phe
                3235                3240                3245

caa att cct gga tac act gtt cca gtt gtc aat gtt gaa gtg tct cca   9914
Gln Ile Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu Val Ser Pro
            3250                3255                3260


ttc acc ata gag atg tcg gca ttc ggc tat gtg ttc cca aaa gca gtc   9962
Phe Thr Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro Lys Ala Val
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      3265                3270                3275

agc atg cct agt ttc tcc atc cta ggt tct gac gtc cgt gtg cct tca   10010
Ser Met Pro Ser Phe Ser Ile Leu Gly Ser Asp Val Arg Val Pro Ser
    3280                3285                3290

tac aca tta atc ctg cca tca tta gag ctg cca gtc ctt cat gtc cct   10058
Tyr Thr Leu Ile Leu Pro Ser Leu Glu Leu Pro Val Leu His Val Pro
3295                3300                3305                3310

aga aat ctc aag ctt tct ctt cca cat ttc aag gaa ttg tgt acc ata   10106
Arg Asn Leu Lys Leu Ser Leu Pro His Phe Lys Glu Leu Cys Thr Ile
                3315                3320                3325

agc cat att ttt att cct gcc atg ggc aat att acc tat gat ttc tcc   10154
Ser His Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr Asp Phe Ser
            3330                3335                3340

ttt aaa tca agt gtc atc aca ctg aat acc aat gct gaa ctt ttt aac   10202
Phe Lys Ser Ser Val Ile Thr Leu Asn Thr Asn Ala Glu Leu Phe Asn
        3345                3350                3355

cag tca gat att gtt gct cat ctc ctt tct tca tct tca tct gtc att   10250
Gln Ser Asp Ile Val Ala His Leu Leu Ser Ser Ser Ser Ser Val Ile
    3360                3365                3370

gat gca ctg cag tac aaa tta gag ggc acc aca aga ttg aca aga aaa   10298
Asp Ala Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys
3375                3380                3385                3390

agg gga ttg aag tta gcc aca gct ctg tct ctg agc aac aaa ttt gtg   10346
Arg Gly Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val
                3395                3400                3405

gag ggt agt cat aac agt act gtg agc tta acc acg aaa aat atg gaa   10394
Glu Gly Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu
            3410                3415                3420

gtg tca gtg gca aaa acc aca aaa gcc gaa att cca att ttg aga atg   10442
Val Ser Val Ala Lys Thr Thr Lys Ala Glu Ile Pro Ile Leu Arg Met
        3425                3430                3435

aat ttc aag caa gaa ctt aat gga aat acc aag tca aaa cct act gtc   10490
Asn Phe Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr Val
    3440                3445                3450

tct tcc tcc atg gaa ttt aag tat gat ttc aat tct tca atg ctg tac   10538
Ser Ser Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser Met Leu Tyr
3455                3460                3465                3470

tct acc gct aaa gga gca gtt gac cac aag ctt agc ttg gaa agc ctc   10586
Ser Thr Ala Lys Gly Ala Val Asp His Lys Leu Ser Leu Glu Ser Leu
                3475                3480                3485

acc tct tac ttt tcc att gag tca tct acc aaa gga gat gtc aag ggt   10634
Thr Ser Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asp Val Lys Gly
            3490                3495                3500

tcg gtt ctt tct cgg gaa tat tca gga act att gct agt gag gcc aac   10682
Ser Val Leu Ser Arg Glu Tyr Ser Gly Thr Ile Ala Ser Glu Ala Asn
        3505                3510                3515

act tac ttg aat tcc aag agc aca cgg tct tca gtg aag ctg cag ggc   10730
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Thr Tyr Leu Asn Ser Lys Ser Thr Arg Ser Ser Val Lys Leu Gln Gly
    3520                3525                3530

act tcc aaa att gat gat atc tgg aac ctt gaa gta aaa gaa aat ttt  10778
Thr Ser Lys Ile Asp Asp Ile Trp Asn Leu Glu Val Lys Glu Asn Phe
3535                3540                3545                3550

gct gga gaa gcc aca ctc caa cgc ata tat tcc ctc tgg gag cac agt  10826
Ala Gly Glu Ala Thr Leu Gln Arg Ile Tyr Ser Leu Trp Glu His Ser
                3555                3560                3565

acg aaa aac cac tta cag cta gag ggc ctc ttt ttc acc aac gga gaa  10874
Thr Lys Asn His Leu Gln Leu Glu Gly Leu Phe Phe Thr Asn Gly Glu
            3570                3575                3580

cat aca agc aaa gcc acc ctg gaa ctc tct cca tgg caa atg tca gct  10922
His Thr Ser Lys Ala Thr Leu Glu Leu Ser Pro Trp Gln Met Ser Ala
        3585                3590                3595

ctt gtt cag gtc cat gca agt cag ccc agt tcc ttc cat gat ttc cct  10970
Leu Val Gln Val His Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro
    3600                3605                3610

gac ctt ggc cag gaa gtg gcc ctg aat gct aac act aag aac cag aag  11018
Asp Leu Gly Gln Glu Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys
3615                3620                3625                3630

atc aga tgg aaa aat gaa gtc cgg att cat tct ggg tct ttc cag agc  11066
Ile Arg Trp Lys Asn Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser
                3635                3640                3645

cag gtc gag ctt tcc aat gac caa gaa aag gca cac ctt gac att gca  11114
Gln Val Glu Leu Ser Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala
            3650                3655                3660

gga tcc tta gaa gga cac cta agg ttc ctc aaa aat atc atc cta cca  11162
Gly Ser Leu Glu Gly His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro
        3665                3670                3675

gtc tat gac aag agc tta tgg gat ttc cta aag ctg gat gta acc acc  11210
Val Tyr Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr
    3680                3685                3690

agc att ggt agg aga cag cat ctt cgt gtt tca act gcc ttt gtg tac  11258
Ser Ile Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr
3695                3700                3705                3710

acc aaa aac ccc aat ggc tat tca ttc tcc atc cct gta aaa gtt ttg  11306
Thr Lys Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu
                3715                3720                3725

gct gat aaa ttc att act cct ggg ctg aaa cta aat gat cta aat tca  11354
Ala Asp Lys Phe Ile Thr Pro Gly Leu Lys Leu Asn Asp Leu Asn Ser
            3730                3735                3740

gtt ctt gtc atg cct acg ttc cat gtc cca ttt aca gat ctt cag gtt  11402
Val Leu Val Met Pro Thr Phe His Val Pro Phe Thr Asp Leu Gln Val
        3745                3750                3755
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cca tcg tgc aaa ctt gac ttc aga gaa ata caa atc tat aag aag ctg   11450
Pro Ser Cys Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu
    3760                3765                3770

aga act tca tca ttt gcc ctc aac cta cca aca ctc ccc gag gta aaa   11498
Arg Thr Ser Ser Phe Ala Leu Asn Leu Pro Thr Leu Pro Glu Val Lys
3775                3780                3785                3790

ttc cct gaa gtt gat gtg tta aca aaa tat tct caa cca gaa gac tcc   11546
Phe Pro Glu Val Asp Val Leu Thr Lys Tyr Ser Gln Pro Glu Asp Ser
                3795                3800                3805

ttg att ccc ttt ttt gag ata acc gtg cct gaa tct cag tta act gtg   11594
Leu Ile Pro Phe Phe Glu Ile Thr Val Pro Glu Ser Gln Leu Thr Val
            3810                3815                3820

tcc cag ttc acg ctt cca aaa agt gtt tca gat ggc att gct gct ttg   11642
Ser Gln Phe Thr Leu Pro Lys Ser Val Ser Asp Gly Ile Ala Ala Leu
        3825                3830                3835

gat cta aat gca gta gcc aac aag atc gca gac ttt gag ttg ccc acc   11690
Asp Leu Asn Ala Val Ala Asn Lys Ile Ala Asp Phe Glu Leu Pro Thr
    3840                3845                3850

atc atc gtg cct gag cag acc att gag att ccc tcc att aag ttc tct   11738
Ile Ile Val Pro Glu Gln Thr Ile Glu Ile Pro Ser Ile Lys Phe Ser
3855                3860                3865                3870

gta cct gct gga att gtc att cct tcc ttt caa gca ctg act gca cgc   11786
Val Pro Ala Gly Ile Val Ile Pro Ser Phe Gln Ala Leu Thr Ala Arg
                3875                3880                3885

ttt gag gta gac tct ccc gtg tat aat gcc act tgg agt gcc agt ttg   11834
Phe Glu Val Asp Ser Pro Val Tyr Asn Ala Thr Trp Ser Ala Ser Leu
            3890                3895                3900

aaa aac aaa gca gat tat gtt gaa aca gtc ctg gat tcc aca tgc agc   11882
Lys Asn Lys Ala Asp Tyr Val Glu Thr Val Leu Asp Ser Thr Cys Ser
        3905                3910                3915

tca acc gta cag ttc cta gaa tat gaa cta aat gtt ttg gga aca cac   11930
Ser Thr Val Gln Phe Leu Glu Tyr Glu Leu Asn Val Leu Gly Thr His
    3920                3925                3930

aaa atc gaa gat ggt acg tta gcc tct aag act aaa gga aca ctt gca   11978
Lys Ile Glu Asp Gly Thr Leu Ala Ser Lys Thr Lys Gly Thr Leu Ala
3935                3940                3945                3950

cac cgt gac ttc agt gca gaa tat gaa gaa gat ggc aaa ttt gaa gga   12026
His Arg Asp Phe Ser Ala Glu Tyr Glu Glu Asp Gly Lys Phe Glu Gly
                3955                3960                3965

ctt cag gaa tgg gaa gga aaa gcg cac ctc aat atc aaa agc cca gcg   12074
Leu Gln Glu Trp Glu Gly Lys Ala His Leu Asn Ile Lys Ser Pro Ala
            3970                3975                3980

ttc acc gat ctc cat ctg cgc tac cag aaa gac aag aaa ggc atc tcc   12122
Phe Thr Asp Leu His Leu Arg Tyr Gln Lys Asp Lys Lys Gly Ile Ser
        3985                3990                3995

acc tca gca gcc tcc cca gcc gta ggc acc gtg ggc atg gat atg gat   12170
Thr Ser Ala Ala Ser Pro Ala Val Gly Thr Val Gly Met Asp Met Asp
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4000                4005                4010

gaa gat gac gac ttt tct aaa tgg aac ttc tac tac agc cct cag tcc   12218
Glu Asp Asp Asp Phe Ser Lys Trp Asn Phe Tyr Tyr Ser Pro Gln Ser
4015                4020                4025                4030

tct cca gat aaa aaa ctc acc ata ttc aaa act gag ttg agg gtc cgg   12266
Ser Pro Asp Lys Lys Leu Thr Ile Phe Lys Thr Glu Leu Arg Val Arg
                4035                4040                4045

gaa tct gat gag gaa act cag atc aaa gtt aat tgg gaa gaa gag gca   12314
Glu Ser Asp Glu Glu Thr Gln Ile Lys Val Asn Trp Glu Glu Glu Ala
            4050                4055                4060

gct tct ggc ttg cta acc tct ctg aaa gac aac gtg ccc aag gcc aca   12362
Ala Ser Gly Leu Leu Thr Ser Leu Lys Asp Asn Val Pro Lys Ala Thr
        4065                4070                4075

ggg gtc ctt tat gat tat gtc aac aag tac cac tgg gaa cac aca ggg   12410
Gly Val Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly
    4080                4085                4090

ctc acc ctg aga gaa gtg tct tca aag ctg aga aga aat ctg cag aac   12458
Leu Thr Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn
4095                4100                4105                4110

aat gct gag tgg gtt tat caa ggg gcc att agg caa att gat gat atc   12506
Asn Ala Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile
                4115                4120                4125

gac gtg agg ttc cag aaa gca gcc agt ggc acc act ggg acc tac caa   12554
Asp Val Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly Thr Tyr Gln
            4130                4135                4140

gag tgg aag gac aag gcc cag aat ctg tac cag gaa ctg ttg act cag   12602
Glu Trp Lys Asp Lys Ala Gln Asn Leu Tyr Gln Glu Leu Leu Thr Gln
        4145                4150                4155

gaa ggc caa gcc agt ttc cag gga ctc aag gat aac gtg ttt gat ggc   12650
Glu Gly Gln Ala Ser Phe Gln Gly Leu Lys Asp Asn Val Phe Asp Gly
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ttg gta cga gtt act caa aaa ttc cat atg aaa gtc aag cat ctg att   12698
Leu Val Arg Val Thr Gln Lys Phe His Met Lys Val Lys His Leu Ile
4175                4180                4185                4190

gac tca ctc att gat ttt ctg aac ttc ccc aga ttc cag ttt ccg ggg   12746
Asp Ser Leu Ile Asp Phe Leu Asn Phe Pro Arg Phe Gln Phe Pro Gly
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aaa cct ggg ata tac act agg gag gaa ctt tgc act atg ttc ata agg   12794
Lys Pro Gly Ile Tyr Thr Arg Glu Glu Leu Cys Thr Met Phe Ile Arg
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gag gta ggg acg gta ctg tcc cag gta tat tcg aaa gtc cat aat ggt   12842
Glu Val Gly Thr Val Leu Ser Gln Val Tyr Ser Lys Val His Asn Gly
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tca gaa ata ctg ttt tcc tat ttc caa gac cta gtg att aca ctt cct   12890
Ser Glu Ile Leu Phe Ser Tyr Phe Gln Asp Leu Val Ile Thr Leu Pro
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ttc gag tta agg aaa cat aaa cta ata gat gta atc tcg atg tat agg   12938
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Phe Glu Leu Arg Lys His Lys Leu Ile Asp Val Ile Ser Met Tyr Arg
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Glu Leu Leu Lys Asp Leu Ser Lys Glu Ala Gln Glu Val Phe Lys Ala
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att cag tct ctc aag acc aca gag gtg cta cgt aat ctt cag gac ctt   13034
Ile Gln Ser Leu Lys Thr Thr Glu Val Leu Arg Asn Leu Gln Asp Leu
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tta caa ttc att ttc caa cta ata gaa gat aac att aaa cag ctg aaa   13082
Leu Gln Phe Ile Phe Gln Leu Ile Glu Asp Asn Ile Lys Gln Leu Lys
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gag atg aaa ttt act tat ctt att aat tat atc caa gat gag atc aac   13130
Glu Met Lys Phe Thr Tyr Leu Ile Asn Tyr Ile Gln Asp Glu Ile Asn
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aca atc ttc aat gat tat atc cca tat gtt ttt aaa ttg ttg aaa gaa   13178
Thr Ile Phe Asn Asp Tyr Ile Pro Tyr Val Phe Lys Leu Leu Lys Glu
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aac cta tgc ctt aat ctt cat aag ttc aat gaa ttt att caa aac gag   13226
Asn Leu Cys Leu Asn Leu His Lys Phe Asn Glu Phe Ile Gln Asn Glu
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ctt cag gaa gct tct caa gag tta cag cag atc cat caa tac att atg   13274
Leu Gln Glu Ala Ser Gln Glu Leu Gln Gln Ile His Gln Tyr Ile Met
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gcc ctt cgt gaa gaa tat ttt gat cca agt ata gtt ggc tgg aca gtg   13322
Ala Leu Arg Glu Glu Tyr Phe Asp Pro Ser Ile Val Gly Trp Thr Val
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aaa tat tat gaa ctt gaa gaa aag ata gtc agt ctg atc aag aac ctg   13370
Lys Tyr Tyr Glu Leu Glu Glu Lys Ile Val Ser Leu Ile Lys Asn Leu
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tta gtt gct ctt aag gac ttc cat tct gaa tat att gtc agt gcc tct   13418
Leu Val Ala Leu Lys Asp Phe His Ser Glu Tyr Ile Val Ser Ala Ser
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Asn Phe Thr Ser Gln Leu Ser Ser Gln Val Glu Gln Phe Leu His Arg
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Asn Ile Gln Glu Tyr Leu Ser Ile Leu Thr Asp Pro Asp Gly Lys Gly
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Lys Glu Lys Ile Ala Glu Leu Ser Ala Thr Ala Gln Glu Ile Ile Lys
        4465                4470                4475

agc cag gcc att gcg acg aag aaa ata att tct gat tac cac cag cag   13610
Ser Gln Ala Ile Ala Thr Lys Lys Ile Ile Ser Asp Tyr His Gln Gln
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Phe Arg Tyr Lys Leu Gln Asp Phe Ser Asp Gln Leu Ser Asp Tyr Tyr
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Asn Tyr His Thr Phe Leu Ile Tyr Ile Thr Glu Leu Leu Lys Lys Leu
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4545 4550 4555

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Leu Thr Ile Ile Leu *
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Glu Asn Val Ser Leu Val Cys Pro Lys Asp Ala Thr Arg Phe Lys His
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Leu Arg Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu Ser Ser Ser Gly Val
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Pro Gly Thr Ala Asp Ser Arg Ser Ala Thr Arg Ile Asn Cys Lys Val
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85 90 95

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Cys Thr Leu Lys Glu Val Tyr Gly Phe Asn Pro Glu Gly Lys Ala Leu
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Ile Ser Ala Leu Leu Val Pro Pro Glu Thr Glu Glu Ala Lys Gln Val
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Leu Phe Leu Asp Thr Val Tyr Gly Asn Cys Ser Thr His Phe Thr Val
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aag acg agg aag ggc aat gtg gca aca gaa ata tcc act gaa aga gac   624
Lys Thr Arg Lys Gly Asn Val Ala Thr Glu Ile Ser Thr Glu Arg Asp
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Leu Gly Gln Cys Asp Arg Phe Lys Pro Ile Arg Thr Gly Ile Ser Pro
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Ser Ser Gln Ser Cys Gln Tyr Thr Leu Asp Ala Lys Arg Lys His Val
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Ala Glu Ala Ile Cys Lys Glu Gln His Leu Phe Leu Pro Phe Ser Tyr
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aag aat aag tat ggg atg gta gca caa gtg aca cag act ttg aaa ctt   864
Lys Asn Lys Tyr Gly Met Val Ala Gln Val Thr Gln Thr Leu Lys Leu
        275                 280                 285

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Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe Gly Glu Gly Thr Lys
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Lys Met Gly Leu Ala Phe Glu Ser Thr Lys Ser Thr Ser Pro Pro Lys
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cag gcc gaa gct gtt ttg aag act ctc cag gaa ctg aaa aaa cta acc   1008
Gln Ala Glu Ala Val Leu Lys Thr Leu Gln Glu Leu Lys Lys Leu Thr
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Ile Ser Glu Gln Asn Ile Gln Arg Ala Asn Leu Phe Asn Lys Leu Val
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Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu Gln Ala Leu Val Gln
    370                 375                 380

tgt gga cag cct cag tgc tcc act cac atc ctc cag tgg ctg aaa cgt   1200
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Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu Gln Trp Leu Lys Arg
385                 390                 395                 400

gtg cat gcc aac ccc ctt ctg ata gat gtg gtc acc tac ctg gtg gcc   1248
Val His Ala Asn Pro Leu Leu Ile Asp Val Val Thr Tyr Leu Val Ala
                405                 410                 415

ctg atc ccc gag ccc tca gca cag cag ctg cga gag atc ttc aac atg   1296
Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg Glu Ile Phe Asn Met
            420                 425                 430

gcg agg gat cag cgc agc cga gcc acc ttg tat gcg ctg agc cac gcg   1344
Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr Ala Leu Ser His Ala
        435                 440                 445

gtc aac aac tat cat aag aca aac cct aca ggg acc cag gag ctg ctg   1392
Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly Thr Gln Glu Leu Leu
    450                 455                 460

gac att gct aat tac ctg atg gaa cag att caa gat gac tgc act ggg   1440
Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln Asp Asp Cys Thr Gly
465                 470                 475                 480

gat gaa gat tac acc tat ttg att ctg cgg gtc att gga aat atg ggc   1488
Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val Ile Gly Asn Met Gly
                485                 490                 495

caa acc atg gag cag tta act cca gaa ctc aag tct tca atc ctg aaa   1536
Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys Ser Ser Ile Leu Lys
            500                 505                 510

tgt gtc caa agt aca aag cca tca ctg atg atc cag aaa gct gcc atc   1584
Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile Gln Lys Ala Ala Ile
        515                 520                 525

cag gct ctg cgg aaa atg gag cct aaa gac aag gac cag gag gtt ctt   1632
Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys Asp Gln Glu Val Leu
    530                 535                 540

ctt cag act ttc ctt gat gat gct tct ccg gga gat aag cga ctg gct   1680
Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly Asp Lys Arg Leu Ala
545                 550                 555                 560

gcc tat ctt atg ttg atg agg agt cct tca cag gca gat att aac aaa   1728
Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln Ala Asp Ile Asn Lys
                565                 570                 575

att gtc caa att cta cca tgg gaa cag aat gag caa gtg aag aac ttt   1776
Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu Gln Val Lys Asn Phe
            580                 585                 590

gtg gct tcc cat att gcc aat atc ttg aac tca gaa gaa ttg gat atc   1824
Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser Glu Glu Leu Asp Ile
        595                 600                 605

caa gat ctg aaa aag tta gtg aaa gaa gct ctg aaa gaa tct caa ctt   1872
Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu Lys Glu Ser Gln Leu
    610                 615                 620

cca act gtc atg gac ttc aga aaa ttc tct cgg aac tat caa ctc tac   1920
Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg Asn Tyr Gln Leu Tyr
625                 630                 635                 640
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aaa tct gtt tct ctt cca tca ctt gac cca gcc tca gcc aaa ata gaa   1968
Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala Ser Ala Lys Ile Glu
                645                 650                 655

ggg aat ctt ata ttt gat cca aat aac tac ctt cct aaa gaa agc atg   2016
Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu Pro Lys Glu Ser Met
            660                 665                 670

ctg aaa act acc ctc act gcc ttt gga ttt gct tca gct gac ctc atc   2064
Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala Ser Ala Asp Leu Ile
        675                 680                 685

gag att ggc ttg gaa gga aaa ggc ttt gag cca aca ttg gag gct cct   2112
Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro Thr Leu Glu Ala Pro
    690                 695                 700

ttt ggg aag caa gga ttt ttc cca gac agt gtc aac aaa gct ttg tac   2160
Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val Asn Lys Ala Leu Tyr
705                 710                 715                 720

tgg gtt aat ggt caa gtt cct gat ggt gtc tct aag gtc tta gtg gac   2208
Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser Lys Val Leu Val Asp
                725                 730                 735

cac ttt ggc tat acc aaa gat gat aaa cat gag cag gat atg gta aat   2256
His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu Gln Asp Met Val Asn
            740                 745                 750

gga ata atg ctc agt gtt gag aag ctg att aaa gat ttg aaa tcc aaa   2304
Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys Asp Leu Lys Ser Lys
        755                 760                 765

gaa gtc ccg gaa gcc aga gcc tac ctc cgc atc ttg gga gag gag ctt   2352
Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile Leu Gly Glu Glu Leu
    770                 775                 780

ggt ttt gcc agt ctc cat gac ctc cga ctc ctg gga aag ctg ctt ctg   2400
Gly Phe Ala Ser Leu His Asp Leu Arg Leu Leu Gly Lys Leu Leu Leu
785                 790                 795                 800

atg ggt gcc cgc act ctg cag ggg atc ccc cag atg att gga gag gtc   2448
Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln Met Ile Gly Glu Val
                805                 810                 815

atc agg aag ggc tca aag aat gac ttt ttt ctt cac tac atc ttc atg   2496
Ile Arg Lys Gly Ser Lys Asn Asp Phe Phe Leu His Tyr Ile Phe Met
            820                 825                 830

gag aat gcc ttt gaa ctc ccc act gga gct gga tta cag ttg caa ata   2544
Glu Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly Leu Gln Leu Gln Ile
        835                 840                 845

tct tca tct gga gtc att gct ccc gga gcc aag gct gga gta aaa ctg   2592
Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys Ala Gly Val Lys Leu
    850                 855                 860

gaa gta gcc aac atg cag gct gaa ctg gtg gca aaa ccc tcc gtg tct   2640
Glu Val Ala Asn Met Gln Ala Glu Leu Val Ala Lys Pro Ser Val Ser
865                 870                 875                 880

gtg gag ttt gtg aca aat atg ggc atc atc att ccg gac ttc gct agg   2688
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Val Glu Phe Val Thr Asn Met Gly Ile Ile Ile Pro Asp Phe Ala Arg
                885                 890                 895

agt ggg gtc cag atg aac acc aac ttc ttc cac gag tcg ggt ctg gag   2736
Ser Gly Val Gln Met Asn Thr Asn Phe Phe His Glu Ser Gly Leu Glu
            900                 905                 910

gct cat gtt gcc cta aaa gct ggg aag ctg aag ttt atc att cct tcc   2784
Ala His Val Ala Leu Lys Ala Gly Lys Leu Lys Phe Ile Ile Pro Ser
        915                 920                 925

cca aag aga cca gtc aag ctg ctc agt gga ggc aac aca tta cat ttg   2832
Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly Asn Thr Leu His Leu
    930                 935                 940

gtc tct acc acc aaa acg gag gtc atc cca cct ctc att gag aac agg   2880
Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro Leu Ile Glu Asn Arg
945                 950                 955                 960

cag tcc tgg tca gtt tgc aag caa gtc ttt cct ggc ctg aat tac tgc   2928
Gln Ser Trp Ser Val Cys Lys Gln Val Phe Pro Gly Leu Asn Tyr Cys
                965                 970                 975

acc tca ggc gct tac tcc aac gcc agc tcc aca gac tcc gcc tcc tac   2976
Thr Ser Gly Ala Tyr Ser Asn Ala Ser Ser Thr Asp Ser Ala Ser Tyr
            980                 985                 990

tat ccg ctg acc ggg gac acc aga tta gag ctg gaa ctg agg cct acg   3024
Tyr Pro Leu Thr Gly Asp Thr Arg Leu Glu Leu Glu Leu Arg Pro Thr
        995                1000                1005

gga gag att gag cag tat tct gtc agc gca acc tat gag ctc cag aga   3072
Gly Glu Ile Glu Gln Tyr Ser Val Ser Ala Thr Tyr Glu Leu Gln Arg
    1010                1015                1020

gag gac aga gcc ttg gtg gat acc ctg aag ttt gta act caa gca gaa   3120
Glu Asp Arg Ala Leu Val Asp Thr Leu Lys Phe Val Thr Gln Ala Glu
1025                1030                1035                1040

ggc gcg aag cag act gag gct acc atg aca ttc aaa tat aat cgg cag   3168
Gly Ala Lys Gln Thr Glu Ala Thr Met Thr Phe Lys Tyr Asn Arg Gln
                1045                1050                1055

agt atg acc ttg tcc agt gaa gtc caa att ccg gat ttt gat gtt gac   3216
Ser Met Thr Leu Ser Ser Glu Val Gln Ile Pro Asp Phe Asp Val Asp
            1060                1065                1070

ctc gga aca atc ctc aga gtt aat gat gaa tct act gag ggc aaa acg   3264
Leu Gly Thr Ile Leu Arg Val Asn Asp Glu Ser Thr Glu Gly Lys Thr
        1075                1080                1085

tct tac aga ctc acc ctg gac att cag aac aag aaa att act gag gtc   3312
Ser Tyr Arg Leu Thr Leu Asp Ile Gln Asn Lys Lys Ile Thr Glu Val
    1090                1095                1100

gcc ctc atg ggc cac cta agt tgt gac aca aag gaa gaa aga aaa atc   3360
Ala Leu Met Gly His Leu Ser Cys Asp Thr Lys Glu Glu Arg Lys Ile
1105                1110                1115                1120

aag ggt gtt att tcc ata ccc cgt ttg caa gca gaa gcc aga agt gag   3408
Lys Gly Val Ile Ser Ile Pro Arg Leu Gln Ala Glu Ala Arg Ser Glu
                1125                1130                1135
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atc ctc gcc cac tgg tcg cct gcc aaa ctg ctt ctc caa atg gac tca   3456
Ile Leu Ala His Trp Ser Pro Ala Lys Leu Leu Gln Met Asp Ser
            1140                1145                1150

tct gct aca gct tat ggc tcc aca gtt tcc aag agg gtg gca tgg cat   3504
Ser Ala Thr Ala Tyr Gly Ser Thr Val Ser Lys Arg Val Ala Trp His
        1155                1160                1165

tat gat gaa gag aag att gaa ttt gaa tgg aac aca ggc acc aat gta   3552
Tyr Asp Glu Glu Lys Ile Glu Phe Glu Trp Asn Thr Gly Thr Asn Val
    1170                1175                1180

gat acc aaa aaa atg act tcc aat ttc cct gtg gat ctc tcc gat tat   3600
Asp Thr Lys Lys Met Thr Ser Asn Phe Pro Val Asp Leu Ser Asp Tyr
1185                1190                1195                1200

cct aag agc ttg cat atg tat gct aat aga ctc ctg gat cac aga gtc   3648
Pro Lys Ser Leu His Met Tyr Ala Asn Arg Leu Leu Asp His Arg Val
                1205                1210                1215

cct caa aca gac atg act ttc cgg cac gtg ggt tcc aaa tta ata gtt   3696
Pro Gln Thr Asp Met Thr Phe Arg His Val Gly Ser Lys Leu Ile Val
            1220                1225                1230

gca atg agc tca tgg ctt cag aag gca tct ggg agt ctt cct tat acc   3744
Ala Met Ser Ser Trp Leu Gln Lys Ala Ser Gly Ser Leu Pro Tyr Thr
        1235                1240                1245

cag act ttg caa gac cac ctc aat agc ctg aag gag ttc aac ctc cag   3792
Gln Thr Leu Gln Asp His Leu Asn Ser Leu Lys Glu Phe Asn Leu Gln
    1250                1255                1260

aac atg gga ttg cca gac tcc cac atc cca gaa aac ctc ttc tta aaa   3840
Asn Met Gly Leu Pro Asp Ser His Ile Pro Glu Asn Leu Phe Leu Lys
1265                1270                1275                1280

agc gat ggc cgc gtc aaa tat acc ttg aac aag aac agt ttg aaa att   3888
Ser Asp Gly Arg Val Lys Tyr Thr Leu Asn Lys Asn Ser Leu Lys Ile
                1285                1290                1295

gag att cct ttg cct ttt ggt ggc aaa tcc tcc aga gat cta aag atg   3936
Glu Ile Pro Leu Pro Phe Gly Gly Lys Ser Ser Arg Asp Leu Lys Met
            1300                1305                1310

tta gag act gtt agg aca cca gcc ctc cac ttc aag tct gtg gga ttc   3984
Leu Glu Thr Val Arg Thr Pro Ala Leu His Phe Lys Ser Val Gly Phe
        1315                1320                1325

cat ctg cca tct cga gag ttc caa gtc cct act ttt acc att ccc aag   4032
His Leu Pro Ser Arg Glu Phe Gln Val Pro Thr Phe Thr Ile Pro Lys
    1330                1335                1340

ttg tat caa ctg caa gtg cct ctc ctg ggt gtt cta gac ctc tcc acg   4080
Leu Tyr Gln Leu Gln Val Pro Leu Leu Gly Val Leu Asp Leu Ser Thr
1345                1350                1355                1360

aat gtc tac agc aac ttg tac aac tgg tcc gcc tcc tac agt ggt ggc   4128
Asn Val Tyr Ser Asn Leu Tyr Asn Trp Ser Ala Ser Tyr Ser Gly Gly
                1365                1370                1375

aac acc agc aca gac cat ttc agc ctt cgg gct cgt tac cac atg aag   4176
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Asn Thr Ser Thr Asp His Phe Ser Leu Arg Ala Arg Tyr His Met Lys
            1380                1385                1390

gct gac tct gtg gtt gac ctg ctt tcc tac aat gtg caa gga tct gga   4224
Ala Asp Ser Val Val Asp Leu Leu Ser Tyr Asn Val Gln Gly Ser Gly
        1395                1400                1405

gaa aca aca tat gac cac aag aat acg ttc aca cta tca tgt gat ggg   4272
Glu Thr Thr Tyr Asp His Lys Asn Thr Phe Thr Leu Ser Cys Asp Gly
    1410                1415                1420

tct cta cgc cac aaa ttt cta gat tcg aat atc aaa ttc agt cat gta   4320
Ser Leu Arg His Lys Phe Leu Asp Ser Asn Ile Lys Phe Ser His Val
1425                1430                1435                1440

gaa aaa ctt gga aac aac cca gtc tca aaa ggt tta cta ata ttc gat   4368
Glu Lys Leu Gly Asn Asn Pro Val Ser Lys Gly Leu Leu Ile Phe Asp
                1445                1450                1455

gca tct agt tcc tgg gga cca cag atg tct gct tca gtt cat ttg gac   4416
Ala Ser Ser Ser Trp Gly Pro Gln Met Ser Ala Ser Val His Leu Asp
            1460                1465                1470

tcc aaa aag aaa cag cat ttg ttt gtc aaa gaa gtc aag att gat ggg   4464
Ser Lys Lys Lys Gln His Leu Phe Val Lys Glu Val Lys Ile Asp Gly
        1475                1480                1485

cag ttc aga gtc tct tcg ttc tat gct aaa ggc aca tat ggc ctg tct   4512
Gln Phe Arg Val Ser Ser Phe Tyr Ala Lys Gly Thr Tyr Gly Leu Ser
    1490                1495                1500

tgt cag agg gat cct aac act ggc cgg ctc aat gga gag tcc aac ctg   4560
Cys Gln Arg Asp Pro Asn Thr Gly Arg Leu Asn Gly Glu Ser Asn Leu
1505                1510                1515                1520

agg ttt aac tcc tcc tac ctc caa ggc acc aac cag ata aca gga aga   4608
Arg Phe Asn Ser Ser Tyr Leu Gln Gly Thr Asn Gln Ile Thr Gly Arg
                1525                1530                1535

tat gaa gat gga acc ctc tcc ctc acc tcc acc tct gat ctg caa agt   4656
Tyr Glu Asp Gly Thr Leu Ser Leu Thr Ser Thr Ser Asp Leu Gln Ser
            1540                1545                1550

ggc atc att aaa aat act gct tcc cta aag tat gag aac tac gag ctg   4704
Gly Ile Ile Lys Asn Thr Ala Ser Leu Lys Tyr Glu Asn Tyr Glu Leu
        1555                1560                1565

act tta aaa tct gac acc aat ggg aag tat aag aac ttt gcc act tct   4752
Thr Leu Lys Ser Asp Thr Asn Gly Lys Tyr Lys Asn Phe Ala Thr Ser
    1570                1575                1580

aac aag atg gat atg acc ttc tct aag caa aat gca ctg ctg cgt tct   4800
Asn Lys Met Asp Met Thr Phe Ser Lys Gln Asn Ala Leu Leu Arg Ser
1585                1590                1595                1600


gaa tat cag gct gat tac gag tca ttg agg ttc ttc agc ctg ctt tct   4848
Glu Tyr Gln Ala Asp Tyr Glu Ser Leu Arg Phe Phe Ser Leu Leu Ser
                1605                1610                1615

gga tca cta aat tcc cat ggt ctt gag tta aat gct gac atc tta ggc   4896
Gly Ser Leu Asn Ser His Gly Leu Glu Leu Asn Ala Asp Ile Leu Gly
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                1620                1625                1630

act gac aaa att aat agt ggt gct cac aag gcg aca cta agg att ggc   4944
Thr Asp Lys Ile Asn Ser Gly Ala His Lys Ala Thr Leu Arg Ile Gly
        1635                1640                1645

caa gat gga ata tct acc agt gca acg acc aac ttg aag tgt agt ctc   4992
Gln Asp Gly Ile Ser Thr Ser Ala Thr Thr Asn Leu Lys Cys Ser Leu
    1650                1655                1660

ctg gtg ctg gag aat gag ctg aat gca gag ctt ggc ctc tct ggg gca   5040
Leu Val Leu Glu Asn Glu Leu Asn Ala Glu Leu Gly Leu Ser Gly Ala
1665                1670                1675                1680

tct atg aaa tta aca aca aat ggc cgc ttc agg gaa cac aat gca aaa   5088
Ser Met Lys Leu Thr Thr Asn Gly Arg Phe Arg Glu His Asn Ala Lys
                1685                1690                1695

ttc agt ctg gat ggg aaa gcc gcc ctc aca gag cta tca ctg gga agt   5136
Phe Ser Leu Asp Gly Lys Ala Ala Leu Thr Glu Leu Ser Leu Gly Ser
            1700                1705                1710

gct tat cag gcc atg att ctg ggt gtc gac agc aaa aac att ttc aac   5184
Ala Tyr Gln Ala Met Ile Leu Gly Val Asp Ser Lys Asn Ile Phe Asn
        1715                1720                1725

ttc aag gtc agt caa gaa gga ctt aag ctc tca aat gac atg atg ggc   5232
Phe Lys Val Ser Gln Glu Gly Leu Lys Leu Ser Asn Asp Met Met Gly
    1730                1735                1740

tca tat gct gaa atg aaa ttt gac cac aca aac agt ctg aac att gca   5280
Ser Tyr Ala Glu Met Lys Phe Asp His Thr Asn Ser Leu Asn Ile Ala
1745                1750                1755                1760

ggc tta tca ctg gac ttc tct tca aaa ctt gac aac att tac agc tct   5328
Gly Leu Ser Leu Asp Phe Ser Ser Lys Leu Asp Asn Ile Tyr Ser Ser
                1765                1770                1775

gac aag ttt tat aag caa act gtt aat tta cag cta cag ccc tat tct   5376
Asp Lys Phe Tyr Lys Gln Thr Val Asn Leu Gln Leu Gln Pro Tyr Ser
            1780                1785                1790

ctg gta act act tta aac agt gac ctg aaa tac aat gct ctg gat ctc   5424
Leu Val Thr Thr Leu Asn Ser Asp Leu Lys Tyr Asn Ala Leu Asp Leu
        1795                1800                1805

acc aac aat ggg aaa cta cgg cta gaa ccc ctg aag ctg cat gtg gct   5472
Thr Asn Asn Gly Lys Leu Arg Leu Glu Pro Leu Lys Leu His Val Ala
    1810                1815                1820

ggt aac cta aaa gga gcc tac caa aat aat gaa ata aaa cac atc tat   5520
Gly Asn Leu Lys Gly Ala Tyr Gln Asn Asn Glu Ile Lys His Ile Tyr
1825                1830                1835                1840

gcc atc tct tct gct gcc tta tca gca agc tat aaa gca gac act gtt   5568
Ala Ile Ser Ser Ala Ala Leu Ser Ala Ser Tyr Lys Ala Asp Thr Val
                1845                1850                1855

gct aag gtt cag ggt gtg gag ttt agc cat ggg ctc aac aca gac atc   5616
Ala Lys Val Gln Gly Val Glu Phe Ser His Gly Leu Asn Thr Asp Ile
            1860                1865                1870

gct ggg ctg gct tca gcc att gac atg agc aca aac tat aat tca gac   5664
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Ala Gly Leu Ala Ser Ala Ile Asp Met Ser Thr Asn Tyr Asn Ser Asp
        1875                1880                1885

tca ctg cat ttc agc aat gtc ttc cgt tct gta atg gcc ccg ttt acc   5712
Ser Leu His Phe Ser Asn Val Phe Arg Ser Val Met Ala Pro Phe Thr
    1890                1895                1900

atg acc atc gat gca cat aca aat ggc aat ggg aaa ctc gct ctc tgg   5760
Met Thr Ile Asp Ala His Thr Asn Gly Asn Gly Lys Leu Ala Leu Trp
1905                1910                1915                1920

gga gaa cat act ggg cag ctg tat agc aaa ttc ctg ttg aaa gca gaa   5808
Gly Glu His Thr Gly Gln Leu Tyr Ser Lys Phe Leu Leu Lys Ala Glu
                1925                1930                1935

cct ctg gca ttt act ttc tct cat gat tac aaa ggc tcc aca agt cat   5856
Pro Leu Ala Phe Thr Phe Ser His Asp Tyr Lys Gly Ser Thr Ser His
            1940                1945                1950

cat ctc gtg tct agg aaa agc atc agt gca gct ctt gaa cac aaa gtc   5904
His Leu Val Ser Arg Lys Ser Ile Ser Ala Ala Leu Glu His Lys Val
        1955                1960                1965

agt gcc ctg ctt act cca gct gag cag aca ggc acc tgg aaa ctc aag   5952
Ser Ala Leu Leu Thr Pro Ala Glu Gln Thr Gly Thr Trp Lys Leu Lys
    1970                1975                1980

acc caa ttt aac aac aat gaa tac agc cag gac ttg gat gct tac aac   6000
Thr Gln Phe Asn Asn Asn Glu Tyr Ser Gln Asp Leu Asp Ala Tyr Asn
1985                1990                1995                2000

act aaa gat aaa att ggc gtg gag ctt act gga cga act ctg gct gac   6048
Thr Lys Asp Lys Ile Gly Val Glu Leu Thr Gly Arg Thr Leu Ala Asp
                2005                2010                2015

cta act cta cta gac tcc cca att aaa gtg cca ctt tta ctc agt gag   6096
Leu Thr Leu Leu Asp Ser Pro Ile Lys Val Pro Leu Leu Leu Ser Glu
            2020                2025                2030

ccc atc aat atc aat gat gct tta gag atg aga gat gcc gtt gag aag   6144
Pro Ile Asn Ile Asn Asp Ala Leu Glu Met Arg Asp Ala Val Glu Lys
        2035                2040                2045

ccc caa gaa ttt aca att gtt gct ttt gta aag tat gat aaa aac caa   6192
Pro Gln Glu Phe Thr Ile Val Ala Phe Val Lys Tyr Asp Lys Asn Gln
    2050                2055                2060

gat gtt cac tcc att aac ctc cca ttt ttt gag acc ttg caa gaa tat   6240
Asp Val His Ser Ile Asn Leu Pro Phe Phe Glu Thr Leu Gln Glu Tyr
2065                2070                2075                2080

ttt gag agg aat cga caa acc att ata gtt gta ctg gaa aac gta cag   6288
Phe Glu Arg Asn Arg Gln Thr Ile Ile Val Val Leu Glu Asn Val Gln
                2085                2090                2095

aga aac ctg aag cac atc aat att gat caa ttt gta aga aaa tac aga   6336
Arg Asn Leu Lys His Ile Asn Ile Asp Gln Phe Val Arg Lys Tyr Arg
            2100                2105                2110

gca gcc ctg gga aaa ctc cca cag caa gct aat gat tat ctg aat tca   6384
Ala Ala Leu Gly Lys Leu Pro Gln Gln Ala Asn Asp Tyr Leu Asn Ser
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2115 2120 2125

ttc aat tgg gag aga caa gtt tca cat gcc aag gag aaa ctg act gct 6432
Phe Asn Trp Glu Arg Gln Val Ser His Ala Lys Glu Lys Leu Thr Ala
2130 2135 2140

ctc aca aaa aag tat aga att aca gaa aat gat ata caa att gca tta 6480
Leu Thr Lys Lys Tyr Arg Ile Thr Glu Asn Asp Ile Gln Ile Ala Leu
2145 2150 2155 2160

gat gat gcc aaa atc aac ttt aat gaa aaa cta tct caa ctg cag aca 6528
Asp Asp Ala Lys Ile Asn Phe Asn Glu Lys Leu Ser Gln Leu Gln Thr
2165 2170 2175

tat atg ata caa ttt gat cag tat att aaa gat agt tat gat tta cat 6576
Tyr Met Ile Gln Phe Asp Gln Tyr Ile Lys Asp Ser Tyr Asp Leu His
2180 2185 2190

gat ttg aaa ata gct att gct aat att att gat gaa atc att gaa aaa 6624
Asp Leu Lys Ile Ala Ile Ala Asn Ile Ile Asp Glu Ile Ile Glu Lys
2195 2200 2205

tta aaa agt ctt gat gag cac tat cat acc cgt gta aat tta gta aaa 6672
Leu Lys Ser Leu Asp Glu His Tyr His Thr Arg Val Asn Leu Val Lys
2210 2215 2220

aca atc cat gat cta cat ttg ttt att gaa aat att gat ttt aac aaa 6720
Thr Ile His Asp Leu His Leu Phe Ile Glu Asn Ile Asp Phe Asn Lys
2225 2230 2235 2240

agt gga agt agt act gca tcc tgg att caa aat gtg gat act aag tac 6768
Ser Gly Ser Ser Thr Ala Ser Trp Ile Gln Asn Val Asp Thr Lys Tyr
2245 2250 2255

caa atc aga atc cag ata caa gaa aaa ctg cag cag ctt aag aga cac 6816
Gln Ile Arg Ile Gln Ile Gln Glu Lys Leu Gln Gln Leu Lys Arg His
2260 2265 2270

ata cag aat ata gac atc cag cac cta gct gga aag tta aaa caa cac 6864
Ile Gln Asn Ile Asp Ile Gln His Leu Ala Gly Lys Leu Lys Gln His
2275 2280 2285

att gag gct att gat gtt aga gtg ctt tta gat caa ttg gga act aca 6912
Ile Glu Ala Ile Asp Val Arg Val Leu Leu Asp Gln Leu Gly Thr Thr
2290 2295 2300

att tca ttt gaa aga ata aat gat gtt ctt gag cat gtc aaa cac ttt 6960
Ile Ser Phe Glu Arg Ile Asn Asp Val Leu Glu His Val Lys His Phe
2305 2310 2315 2320

gtt ata aat ctt att ggg gat ttt gaa gta gct gag aaa atc aat gcc 7008
Val Ile Asn Leu Ile Gly Asp Phe Glu Val Ala Glu Lys Ile Asn Ala
2325 2330 2335

ttc aga gcc aaa gtc cat gag tta atc gag agg tat gaa gta gac caa 7056
Phe Arg Ala Lys Val His Glu Leu Ile Glu Arg Tyr Glu Val Asp Gln
2340 2345 2350

caa atc cag gtt tta atg gat aaa tta gta gag ttg gcc cac caa tac 7104
Gln Ile Gln Val Leu Met Asp Lys Leu Val Glu Leu Ala His Gln Tyr
2355 2360 2365

aag ttg aag gag act att cag aag cta agc aat gtc cta caa caa gtt 7152

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Lys Leu Lys Glu Thr Ile Gln Lys Leu Ser Asn Val Leu Gln Gln Val
    2370                2375                2380

aag ata aaa gat tac ttt gag aaa ttg gtt gga ttt att gat gat gct  7200
Lys Ile Lys Asp Tyr Phe Glu Lys Leu Val Gly Phe Ile Asp Asp Ala
2385                2390                2395                2400

gtc aag aag ctt aat gaa tta tct ttt aaa aca ttc att gaa gat gtt  7248
Val Lys Lys Leu Asn Glu Leu Ser Phe Lys Thr Phe Ile Glu Asp Val
                2405                2410                2415

aac aaa ttc ctt gac atg ttg ata aag aaa tta aag tca ttt gat tac  7296
Asn Lys Phe Leu Asp Met Leu Ile Lys Lys Leu Lys Ser Phe Asp Tyr
            2420                2425                2430

cac cag ttt gta gat gaa acc aat gac aaa atc cgt gag gtg act cag  7344
His Gln Phe Val Asp Glu Thr Asn Asp Lys Ile Arg Glu Val Thr Gln
        2435                2440                2445

aga ctc aat ggt gaa att cag gct ctg gaa cta cca caa aaa gct gaa  7392
Arg Leu Asn Gly Glu Ile Gln Ala Leu Glu Leu Pro Gln Lys Ala Glu
    2450                2455                2460

gca tta aaa ctg ttt tta gag gaa acc aag gcc aca gtt gca gtg tat  7440
Ala Leu Lys Leu Phe Leu Glu Glu Thr Lys Ala Thr Val Ala Val Tyr
2465                2470                2475                2480

ctg gaa agc cta cag gac acc aaa ata acc tta atc atc aat tgg tta  7488
Leu Glu Ser Leu Gln Asp Thr Lys Ile Thr Leu Ile Ile Asn Trp Leu
                2485                2490                2495

cag gag gct tta agt tca gca tct ttg gct cac atg aag gcc aaa ttc  7536
Gln Glu Ala Leu Ser Ser Ala Ser Leu Ala His Met Lys Ala Lys Phe
            2500                2505                2510

cga gag act cta gaa gat aca cga gac cga atg tat caa atg gac att  7584
Arg Glu Thr Leu Glu Asp Thr Arg Asp Arg Met Tyr Gln Met Asp Ile
        2515                2520                2525

cag cag gaa ctt caa cga tac ctg tct ctg gta ggc cag gtt tat agc  7632
Gln Gln Glu Leu Gln Arg Tyr Leu Ser Leu Val Gly Gln Val Tyr Ser
    2530                2535                2540

aca ctt gtc acc tac att tct gat tgg tgg act ctt gct gct aag aac  7680
Thr Leu Val Thr Tyr Ile Ser Asp Trp Trp Thr Leu Ala Ala Lys Asn
2545                2550                2555                2560

ctt act gac ttt gca gag caa tat tct atc caa gat tgg gct aaa cgt  7728
Leu Thr Asp Phe Ala Glu Gln Tyr Ser Ile Gln Asp Trp Ala Lys Arg
                2565                2570                2575

atg aaa gca ttg gta gag caa ggg ttc act gtt cct gaa atc aag acc  7776
Met Lys Ala Leu Val Glu Gln Gly Phe Thr Val Pro Glu Ile Lys Thr
            2580                2585                2590

atc ctt ggg acc atg cct gcc ttt gaa gtc agt ctt cag gct ctt cag  7824
Ile Leu Gly Thr Met Pro Ala Phe Glu Val Ser Leu Gln Ala Leu Gln
        2595                2600                2605

aaa gct acc ttc cag aca cct gat ttt ata gtc ccc cta aca gat ttg  7872
Lys Ala Thr Phe Gln Thr Pro Asp Phe Ile Val Pro Leu Thr Asp Leu
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2610                2615                2620

agg att cca tca gtt cag ata aac ttc aaa gac tta aaa aat ata aaa   7920
Arg Ile Pro Ser Val Gln Ile Asn Phe Lys Asp Leu Lys Asn Ile Lys
2625                2630                2635                2640

atc cca tcc agg ttt tcc aca cca gaa ttt acc atc ctt aac acc ttc   7968
Ile Pro Ser Arg Phe Ser Thr Pro Glu Phe Thr Ile Leu Asn Thr Phe
                2645                2650                2655

cac att cct tcc ttt aca att gac ttt gta gaa atg aaa gta aag atc   8016
His Ile Pro Ser Phe Thr Ile Asp Phe Val Glu Met Lys Val Lys Ile
            2660                2665                2670

atc aga acc att gac cag atg ctg aac agt gag ctg cag tgg ccc gtt   8064
Ile Arg Thr Ile Asp Gln Met Leu Asn Ser Glu Leu Gln Trp Pro Val
        2675                2680                2685

cca gat ata tat ctc agg gat ctg aag gtg gag gac att cct cta gcg   8112
Pro Asp Ile Tyr Leu Arg Asp Leu Lys Val Glu Asp Ile Pro Leu Ala
    2690                2695                2700

aga atc acc ctg cca gac ttc cgt tta cca gaa atc gca att cca gaa   8160
Arg Ile Thr Leu Pro Asp Phe Arg Leu Pro Glu Ile Ala Ile Pro Glu
2705                2710                2715                2720

ttc ata atc cca act ctc aac ctt aat gat ttt caa gtt cct gac ctt   8208
Phe Ile Ile Pro Thr Leu Asn Leu Asn Asp Phe Gln Val Pro Asp Leu
                2725                2730                2735

cac ata cca gaa ttc cag ctt ccc cac atc tca cac aca att gaa gta   8256
His Ile Pro Glu Phe Gln Leu Pro His Ile Ser His Thr Ile Glu Val
            2740                2745                2750

cct act ttt ggc aag cta tac agt att ctg aaa atc caa tct cct ctt   8304
Pro Thr Phe Gly Lys Leu Tyr Ser Ile Leu Lys Ile Gln Ser Pro Leu
        2755                2760                2765

ttc aca tta gat gca aat gct gac ata ggg aat gga acc acc tca gca   8352
Phe Thr Leu Asp Ala Asn Ala Asp Ile Gly Asn Gly Thr Thr Ser Ala
    2770                2775                2780

aac gaa gca ggt atc gca gct tcc atc act gcc aaa gga gag tcc aaa   8400
Asn Glu Ala Gly Ile Ala Ala Ser Ile Thr Ala Lys Gly Glu Ser Lys
2785                2790                2795                2800

tta gaa gtt ctc aat ttt gat ttt caa gca aat gca caa ctc tca aac   8448
Leu Glu Val Leu Asn Phe Asp Phe Gln Ala Asn Ala Gln Leu Ser Asn
                2805                2810                2815

cct aag att aat ccg ctg gct ctg aag gag tca gtg aag ttc tcc agc   8496
Pro Lys Ile Asn Pro Leu Ala Leu Lys Glu Ser Val Lys Phe Ser Ser
            2820                2825                2830

aag tac ctg aga acg gag cat ggg agt gaa atg ctg ttt ttt gga aat   8544
Lys Tyr Leu Arg Thr Glu His Gly Ser Glu Met Leu Phe Phe Gly Asn
        2835                2840                2845

gct att gag gga aaa tca aac aca gtg gca agt tta cac aca gaa aaa   8592
Ala Ile Glu Gly Lys Ser Asn Thr Val Ala Ser Leu His Thr Glu Lys
    2850                2855                2860

aat aca ctg gag ctt agt aat gga gtg att gtc aag ata aac aat cag   8640
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Asn Thr Leu Glu Leu Ser Asn Gly Val Ile Val Lys Ile Asn Asn Gln
2865                2870                2875                2880

ctt acc ctg gat agc aac act aaa tac ttc cac aaa ttg aac atc ccc   8688
Leu Thr Leu Asp Ser Asn Thr Lys Tyr Phe His Lys Leu Asn Ile Pro
                2885                2890                2895

aaa ctg gac ttc tct agt cag gct gac ctg cgc aac gag atc aag aca   8736
Lys Leu Asp Phe Ser Ser Gln Ala Asp Leu Arg Asn Glu Ile Lys Thr
            2900                2905                2910

ctg ttg aaa gct ggc cac ata gca tgg act tct tct gga aaa ggg tca   8784
Leu Leu Lys Ala Gly His Ile Ala Trp Thr Ser Ser Gly Lys Gly Ser
        2915                2920                2925

tgg aaa tgg gcc tcg ccc aga ttc tca gat gag gga aca cat gaa tca   8832
Trp Lys Trp Ala Ser Pro Arg Phe Ser Asp Glu Gly Thr His Glu Ser
    2930                2935                2940

caa att agt ttc acc ata gaa gga ccc ctc act tcc ttt gga ctg tcc   8880
Gln Ile Ser Phe Thr Ile Glu Gly Pro Leu Thr Ser Phe Gly Leu Ser
2945                2950                2955                2960

aat aag atc aat agc aaa cac cta aga gta aac caa aac ttg gtt tat   8928
Asn Lys Ile Asn Ser Lys His Leu Arg Val Asn Gln Asn Leu Val Tyr
                2965                2970                2975

gaa tct ggc tcc ctc aac ttt tct aaa ctt gaa att caa tca caa gtc   8976
Glu Ser Gly Ser Leu Asn Phe Ser Lys Leu Glu Ile Gln Ser Gln Val
            2980                2985                2990

gat tcc cag cat gtg ggc cac agt gtt cta act gct aaa ggc atg gca   9024
Asp Ser Gln His Val Gly His Ser Val Leu Thr Ala Lys Gly Met Ala
        2995                3000                3005

ctg ttt gga gaa ggg aag gca gag ttt act ggg agg cat gat gct cat   9072
Leu Phe Gly Glu Gly Lys Ala Glu Phe Thr Gly Arg His Asp Ala His
    3010                3015                3020

tta aat gga aag gtt att gga act ttg aaa aat tct ctt ttc ttt tca   9120
Leu Asn Gly Lys Val Ile Gly Thr Leu Lys Asn Ser Leu Phe Phe Ser
3025                3030                3035                3040

gcc cag cca ttt gag atc acg gca tcc aca aac aat gaa ggg aat ttg   9168
Ala Gln Pro Phe Glu Ile Thr Ala Ser Thr Asn Asn Glu Gly Asn Leu
                3045                3050                3055

aaa gtt cgt ttt cca tta agg tta aca ggg aag ata gac ttc ctg aat   9216
Lys Val Arg Phe Pro Leu Arg Leu Thr Gly Lys Ile Asp Phe Leu Asn
            3060                3065                3070

aac tat gca ctg ttt ctg agt ccc agt gcc cag caa gca agt tgg caa   9264
Asn Tyr Ala Leu Phe Leu Ser Pro Ser Ala Gln Gln Ala Ser Trp Gln
        3075                3080                3085

gta agt gct agg ttc aat cag tat aag tac aac caa aat ttc tct gct   9312
Val Ser Ala Arg Phe Asn Gln Tyr Lys Tyr Asn Gln Asn Phe Ser Ala
    3090                3095                3100

gga aac aac gag aac att atg gag gcc cat gta gga ata aat gga gaa   9360
Gly Asn Asn Glu Asn Ile Met Glu Ala His Val Gly Ile Asn Gly Glu
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3105                3110                3115                3120

gca aat ctg gat ttc tta aac att cct tta aca att cct gaa atg cgt   9408
Ala Asn Leu Asp Phe Leu Asn Ile Pro Leu Thr Ile Pro Glu Met Arg
                3125                3130                3135

cta cct tac aca ata atc aca act cct cca ctg aaa gat ttc tct cta   9456
Leu Pro Tyr Thr Ile Ile Thr Thr Pro Pro Leu Lys Asp Phe Ser Leu
            3140                3145                3150

tgg gaa aaa aca ggc ttg aag gaa ttc ttg aaa acg aca aag caa tca   9504
Trp Glu Lys Thr Gly Leu Lys Glu Phe Leu Lys Thr Thr Lys Gln Ser
        3155                3160                3165

ttt gat tta agt gta aaa gct cag tat aag aaa aac aaa cac agg cat   9552
Phe Asp Leu Ser Val Lys Ala Gln Tyr Lys Lys Asn Lys His Arg His
    3170                3175                3180

tcc atc aca aat cct ttg gct gtg ctt tgt gag ttt atc agt cag agc   9600
Ser Ile Thr Asn Pro Leu Ala Val Leu Cys Glu Phe Ile Ser Gln Ser
3185                3190                3195                3200

atc aaa tcc ttt gac agg cat ttt gaa aaa aac aga aac aat gca tta   9648
Ile Lys Ser Phe Asp Arg His Phe Glu Lys Asn Arg Asn Asn Ala Leu
                3205                3210                3215

gat ttt gtc acc aaa tcc tat aat gaa aca aaa att aag ttt gat aag   9696
Asp Phe Val Thr Lys Ser Tyr Asn Glu Thr Lys Ile Lys Phe Asp Lys
            3220                3225                3230

tac aaa gct gaa aaa tct cac gac gag ctc ccc agg acc ttt caa att   9744
Tyr Lys Ala Glu Lys Ser His Asp Glu Leu Pro Arg Thr Phe Gln Ile
        3235                3240                3245

cct gga tac act gtt cca gtt gtc aat gtt gaa gtg tct cca ttc acc   9792
Pro Gly Tyr Thr Val Pro Val Val Asn Val Glu Val Ser Pro Phe Thr
    3250                3255                3260

ata gag atg tcg gca ttc ggc tat gtg ttc cca aaa gca gtc agc atg   9840
Ile Glu Met Ser Ala Phe Gly Tyr Val Phe Pro Lys Ala Val Ser Met
3265                3270                3275                3280

cct agt ttc tcc atc ata ggt tct gac gtc cgt gtg cct tca tac aca   9888
Pro Ser Phe Ser Ile Ile Gly Ser Asp Val Arg Val Pro Ser Tyr Thr
                3285                3290                3295

tta atc ctg cca tca tta gag ctg cca gtc ctt cat gtc cct aga aat   9936
Leu Ile Leu Pro Ser Leu Glu Leu Pro Val Leu His Val Pro Arg Asn
            3300                3305                3310

ctc aag ctt tct ctt cca gat ttc aag gaa ttg tgt acc ata agc cat   9984
Leu Lys Leu Ser Leu Pro Asp Phe Lys Glu Leu Cys Thr Ile Ser His
        3315                3320                3325

att ttt att cct gcc atg ggc aat att acc tat gat ttc tcc ttt aaa  10032
Ile Phe Ile Pro Ala Met Gly Asn Ile Thr Tyr Asp Phe Ser Phe Lys
    3330                3335                3340

tca agt gtc atc aca ctg aat acc aat gct gaa ctt ttt aac cag tca  10080
Ser Ser Val Ile Thr Leu Asn Thr Asn Ala Glu Leu Phe Asn Gln Ser
3345                3350                3355                3360
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gat att gtt gct cat ctc ctt tct tca tct tca tct gtc att gat gca   10128
Asp Ile Val Ala His Leu Leu Ser Ser Ser Ser Ser Val Ile Asp Ala
                3365                3370                3375

ctg cag tac aaa tta gag ggc acc aca aga ttg aca aga aaa agg gga   10176
Leu Gln Tyr Lys Leu Glu Gly Thr Thr Arg Leu Thr Arg Lys Arg Gly
            3380                3385                3390

ttg aag tta gcc aca gct ctg tct ctg agc aac aaa ttt gtg gag ggt   10224
Leu Lys Leu Ala Thr Ala Leu Ser Leu Ser Asn Lys Phe Val Glu Gly
        3395                3400                3405

agt cat aac agt act gtg agc tta acc acg aaa aat atg gaa gtg tca   10272
Ser His Asn Ser Thr Val Ser Leu Thr Thr Lys Asn Met Glu Val Ser
    3410                3415                3420

gtg gca aaa acc aca aaa ccg gaa att cca att ttg aga atg aat ttc   10320
Val Ala Lys Thr Thr Lys Pro Glu Ile Pro Ile Leu Arg Met Asn Phe
3425                3430                3435                3440

aag caa gaa ctt aat gga aat acc aag tca aaa cct act gtc tct tcc   10368
Lys Gln Glu Leu Asn Gly Asn Thr Lys Ser Lys Pro Thr Val Ser Ser
                3445                3450                3455

tcc atg gaa ttt aag tat gat ttc aat tct tca atg ctg tac tct acc   10416
Ser Met Glu Phe Lys Tyr Asp Phe Asn Ser Ser Met Leu Tyr Ser Thr
            3460                3465                3470

gct aaa gga gca gtt gac cac aag ctt agc ttg gaa agc ctc acc tct   10464
Ala Lys Gly Ala Val Asp His Lys Leu Ser Leu Glu Ser Leu Thr Ser
        3475                3480                3485

tac ttt tcc att gag tca tct acc aaa gga gat gtc aag ggt tcg gtt   10512
Tyr Phe Ser Ile Glu Ser Ser Thr Lys Gly Asp Val Lys Gly Ser Val
    3490                3495                3500

ctt tct cgg gaa tat tca gga act att gct agt gag gcc aac act tac   10560
Leu Ser Arg Glu Tyr Ser Gly Thr Ile Ala Ser Glu Ala Asn Thr Tyr
3505                3510                3515                3520

ttg aat tcc aag agc aca cgg tct tca gtg aag ctg cag ggc act tcc   10608
Leu Asn Ser Lys Ser Thr Arg Ser Ser Val Lys Leu Gln Gly Thr Ser
                3525                3530                3535

aaa att gat gat atc tgg aac ctt gaa gta aaa gaa aat ttt gct gga   10656
Lys Ile Asp Asp Ile Trp Asn Leu Glu Val Lys Glu Asn Phe Ala Gly
            3540                3545                3550

gaa gcc aca ctc caa cgc ata tat tcc ctc tgg gag cac agt acg aaa   10704
Glu Ala Thr Leu Gln Arg Ile Tyr Ser Leu Trp Glu His Ser Thr Lys
        3555                3560                3565

aac cac tta cag cta gag ggc ctc ttt ttc acc aac gga gaa cat aca   10752
Asn His Leu Gln Leu Glu Gly Leu Phe Phe Thr Asn Gly Glu His Thr
    3570                3575                3580

agc aaa gcc acc ctg gaa ctc tct cca tgg caa atg tca gct ctt gtt   10800
Ser Lys Ala Thr Leu Glu Leu Ser Pro Trp Gln Met Ser Ala Leu Val
3585                3590                3595                3600

cag gtc cat gca agt cag ccc agt tcc ttc cat gat ttc cct gac ctt   10848
Gln Val His Ala Ser Gln Pro Ser Ser Phe His Asp Phe Pro Asp Leu
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                3605                3610                3615

ggc cag gaa gtg gcc ctg aat gct aac act aag aac cag aag atc aga   10896
Gly Gln Glu Val Ala Leu Asn Ala Asn Thr Lys Asn Gln Lys Ile Arg
            3620                3625                3630

tgg aaa aat gaa gtc cgg att cat tct ggg tct ttc cag agc cag gtc   10944
Trp Lys Asn Glu Val Arg Ile His Ser Gly Ser Phe Gln Ser Gln Val
        3635                3640                3645

gag ctt tcc aat gac caa gaa aag gca cac ctt gac att gca gga tcc   10992
Glu Leu Ser Asn Asp Gln Glu Lys Ala His Leu Asp Ile Ala Gly Ser
    3650                3655                3660

tta gaa gga cac cta agg ttc ctc aaa aat atc atc cta cca gtc tat   11040
Leu Glu Gly His Leu Arg Phe Leu Lys Asn Ile Ile Leu Pro Val Tyr
3665                3670                3675                3680

gac aag agc tta tgg gat ttc cta aag ctg gat gtc acc acc agc att   11088
Asp Lys Ser Leu Trp Asp Phe Leu Lys Leu Asp Val Thr Thr Ser Ile
                3685                3690                3695

ggt agg aga cag cat ctt cgt gtt tca act gcc ttt gtg tac acc aaa   11136
Gly Arg Arg Gln His Leu Arg Val Ser Thr Ala Phe Val Tyr Thr Lys
            3700                3705                3710

aac ccc aat ggc tat tca ttc tcc atc cct gta aaa gtt ttg gct gat   11184
Asn Pro Asn Gly Tyr Ser Phe Ser Ile Pro Val Lys Val Leu Ala Asp
        3715                3720                3725

aaa ttc att att cct ggg ctg aaa cta aat gat cta aat tca gtt ctt   11232
Lys Phe Ile Ile Pro Gly Leu Lys Leu Asn Asp Leu Asn Ser Val Leu
    3730                3735                3740

gtc atg cct acg ttc cat gtc cca ttt aca gat ctt cag gtt cca tcg   11280
Val Met Pro Thr Phe His Val Pro Phe Thr Asp Leu Gln Val Pro Ser
3745                3750                3755                3760

tgc aaa ctt gac ttc aga gaa ata caa atc tat aag aag ctg aga act   11328
Cys Lys Leu Asp Phe Arg Glu Ile Gln Ile Tyr Lys Lys Leu Arg Thr
                3765                3770                3775

tca tca ttt gcc ctc acc cta cca aca ctc ccc gag gta aaa ttc cct   11376
Ser Ser Phe Ala Leu Thr Leu Pro Thr Leu Pro Glu Val Lys Phe Pro
            3780                3785                3790

gaa gtt gat gtg tta aca aaa tat tct caa cca gaa gac tcc ttg att   11424
Glu Val Asp Val Leu Thr Lys Tyr Ser Gln Pro Glu Asp Ser Leu Ile
        3795                3800                3805

ccc ttt ttt gag ata acc gtg cct gaa tct cag tta act gtg tcc cag   11472
Pro Phe Phe Glu Ile Thr Val Pro Glu Ser Gln Leu Thr Val Ser Gln
    3810                3815                3820

ttc acg ctt cca aaa agt gtt tca gat ggc att gct gct ttg gat cta   11520
Phe Thr Leu Pro Lys Ser Val Ser Asp Gly Ile Ala Ala Leu Asp Leu
3825                3830                3835                3840

aat gca gta gcc aac aag atc gca gac ttt gag ttg ccc acc atc atc   11568
Asn Ala Val Ala Asn Lys Ile Ala Asp Phe Glu Leu Pro Thr Ile Ile
                3845                3850                3855
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gtg cct gag cag acc att gag att ccc tcc att aag ttc tct gta cct   11616
Val Pro Glu Gln Thr Ile Glu Ile Pro Ser Ile Lys Phe Ser Val Pro
            3860                3865                3870

gct gga att gtc att cct tcc ttt caa gca ctg act gca cgc ttt gag   11664
Ala Gly Ile Val Ile Pro Ser Phe Gln Ala Leu Thr Ala Arg Phe Glu
        3875                3880                3885

gta gac tct ccc gtg tat aat gcc act tgg agt gcc agt ttg aaa aac   11712
Val Asp Ser Pro Val Tyr Asn Ala Thr Trp Ser Ala Ser Leu Lys Asn
    3890                3895                3900

aaa gca gat tat gtt gaa aca gtc ctg gat tcc aca tgc agc tca acc   11760
Lys Ala Asp Tyr Val Glu Thr Val Leu Asp Ser Thr Cys Ser Ser Thr
3905                3910                3915                3920

gta cag ttc cta gaa tat gaa cta aat gtt ttg gga aca cac aaa atc   11808
Val Gln Phe Leu Glu Tyr Glu Leu Asn Val Leu Gly Thr His Lys Ile
                3925                3930                3935

gaa gat ggt acg tta gcc tct aag act aaa gga aca ctt gca cac cgt   11856
Glu Asp Gly Thr Leu Ala Ser Lys Thr Lys Gly Thr Leu Ala His Arg
            3940                3945                3950

gac ttc agt gca gaa tat gaa gaa gat ggc aaa tat gaa gga ctt cag   11904
Asp Phe Ser Ala Glu Tyr Glu Glu Asp Gly Lys Tyr Glu Gly Leu Gln
        3955                3960                3965

gaa tgg gaa gga aaa gcg cac ctc aat atc aaa agc cca gcg ttc acc   11952
Glu Trp Glu Gly Lys Ala His Leu Asn Ile Lys Ser Pro Ala Phe Thr
    3970                3975                3980

gat ctc cat ctg cgc tac cag aaa gac aag aaa ggc atc tcc acc tca   12000
Asp Leu His Leu Arg Tyr Gln Lys Asp Lys Lys Gly Ile Ser Thr Ser
3985                3990                3995                4000

gca gcc tcc cca gcc gta ggc acc gtg ggc atg gat atg gat gaa gat   12048
Ala Ala Ser Pro Ala Val Gly Thr Val Gly Met Asp Met Asp Glu Asp
                4005                4010                4015

gac gac ttt tct aaa tgg aac ttc tac tac agc cct cag tcc tct cca   12096
Asp Asp Phe Ser Lys Trp Asn Phe Tyr Tyr Ser Pro Gln Ser Ser Pro
            4020                4025                4030

gat aaa aaa ctc acc ata ttc aaa act gag ttg agg gtc cgg gaa tct   12144
Asp Lys Lys Leu Thr Ile Phe Lys Thr Glu Leu Arg Val Arg Glu Ser
        4035                4040                4045

gat gag gaa act cag atc aaa gtt aat tgg gaa gaa gag gca gct tct   12192
Asp Glu Glu Thr Gln Ile Lys Val Asn Trp Glu Glu Glu Ala Ala Ser
    4050                4055                4060

ggc ttg cta acc tct ctg aaa gac aac gtg ccc aag gcc aca ggg gtc   12240
Gly Leu Leu Thr Ser Leu Lys Asp Asn Val Pro Lys Ala Thr Gly Val
4065                4070                4075                4080

ctt tat gat tat gtc aac aag tac cac tgg gaa cac aca ggg ctc acc   12288
Leu Tyr Asp Tyr Val Asn Lys Tyr His Trp Glu His Thr Gly Leu Thr
                4085                4090                4095

ctg aga gaa gtg tct tca aag ctg aga aga aat ctg cag aac aat gct   12336
Leu Arg Glu Val Ser Ser Lys Leu Arg Arg Asn Leu Gln Asn Asn Ala
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          4100                4105                4110

gag tgg gtt tat caa ggg gcc att agg caa att gat gat atc gac gtg   12384
Glu Trp Val Tyr Gln Gly Ala Ile Arg Gln Ile Asp Asp Ile Asp Val
        4115                4120                4125

agg ttc cag aaa gca gcc agt ggc acc act ggg acc tac caa gag tgg   12432
Arg Phe Gln Lys Ala Ala Ser Gly Thr Thr Gly Thr Tyr Gln Glu Trp
    4130                4135                4140

aag gac aag gcc cag aat ctg tac cag gaa ctg ttg act cag gaa ggc   12480
Lys Asp Lys Ala Gln Asn Leu Tyr Gln Glu Leu Leu Thr Gln Glu Gly
4145                4150                4155                4160

caa gcc agt ttc cag gga ctc aag gat aac gtg ttt gat ggc ttg gta   12528
Gln Ala Ser Phe Gln Gly Leu Lys Asp Asn Val Phe Asp Gly Leu Val
                4165                4170                4175

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ggccaaaatg gagtatctac cagtgcaaca accagcttga ggtacagtcc cctgatgctg 240

gagaatgagc tgaacgcaga gcttgccctt tctggggcat ctatgaaatt agcaacaaat 300

ggccgcttca aggaacacaa tgcaaaattc agcctagatg ggaaagctac cctcacagag 360

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cagacatatg tgatataatt tgatcagtat attaaagata attttgatct acatgatttt 240

aaaatagcta tagctagtat tatagatcaa atcatggaaa aattaaaaat tcttgatgaa 300

cgttatcata tccgtgcaca tttaattaaa tcaatccata atttatattt gtttattgaa 360

gctattgatt ttaacaaaat tggaagtagt actgcatctt ggattcaaaa tgtggatacc 420

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agagtgcttt tagatcaatt gagaactaca attccatttc gtataataaa ggacattatt 600

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cctggataca ttattccaat tttcaatntt gaagtatctc cactcacaat agnagacgtn 180

agcattcagt catgtgatcc caaaatcaat aagcaccccc aatgtcacca tcctggattc 240

aagcttctat gtgccttcat atacattggc tctgccatcc ctagagctgc cagtcttcca 300

tgtccccagg aatctactca aggtctctct tccagatttc aaggaattga aaaccattaa 360

caatattttt attccagcca tgggcaacat tacctatgaa ttttccttca aatcaacgat 420

cattacactg aataccaatg ctggacttta taaccaatca gacattgttg cccatatcct 480

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/15493

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07H 21/04

US CL : 536/23.1, 24.3, 24.31, 24/33, 24.5

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.3, 24.31, 24/33, 24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/12789 A2 (CHAN et al.) 22 February 2001 (22.02.2001), page 2, lines 15-27.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 2003 (16.10.2003)	22 OCT 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Janet L. Epps-Ford, Ph.D. Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/15493

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 8-93
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/15493

Continuation of B. FIELDS SEARCHED Item 3:
CAplus, Medline, Biosis, USPAT, EPO, USPG-Pub, JPO, Derwent
search terms:
apolipoprotein B, apoB, antisense, aptamer, triplesx, oligonucleotide, riibozyme, peptide nucleic acid